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MARCH, 1932.

BRAIN.

PART 1, VOL. 55.

A MYOPATHIC FAMILY; WITH HYPERTROPHIC, PSEUDO-HYPERTROPHIC, ATROPHIC AND TERMINAL (DISTAL IN UPPER EXTREMITIES) STAGES.¹

BY STANLEY BARNES.

INTRODUCTION.

SOME ten years ago an unusual type of muscular weakness came under my notice, and it was only after a careful examination that the case was eventually classified as a myopathy. Further inquiry then elicited a family history of "locomotor ataxia," as it was called, going back for several generations. An attempt was therefore made to interview all available descendants of the earliest case (No. 1), who is said to have suffered from "locomotor ataxia," but who died about a century ago. (See Family tree opposite p. 46.)

Many of these persons examined have appeared to be quite normal. Others have shown varying degrees of myopathic weakness; whilst yet others are clearly latent cases of the same disease, in whom a single sign (such as absent knee-jerks or ankle-jerks) is the only evidence of any abnormality.

The total number of descendants of Case 1, who probably was born about 1749 and is known to have died in 1836, is about 500. It has not been possible to obtain such records as were adequate for our purpose in some 200 of these cases, and these have been omitted from the genealogical table. Of those included in the family tree (284 in all), I believe the record is so far correct, either as a result of direct observation or from the detailed description of relatives and others, that it may be accepted for the purpose of determining the form

¹ Presidential Address delivered to the Neurological Section of the Royal Society of Medicine, January 21, 1932.

of inheritance. Altogether over 160 individuals have been personally examined either by my house physicians or myself, and this list includes nearly all the living myopathic members of the group, and all of those who were living in the Midland Counties during the last ten years.

THE FAMILY.

Apart from its affection by myopathy, the family appears to have been free from any unusual tendency to disease in the last 130 years. The various members throughout have remained at the level of the middle class, and have made their way with a sturdy independence without dropping in the social scale. The general level of intelligence is rather above than below the average for their social position, and great determination has been a marked characteristic of some of the later members. In a word, there is no such evidence of social decline or progressive degeneration as has been characteristic of the families of myotonia atrophica recorded by Fleischer, and by Adie and Greenfield; it corresponds more closely in this respect to those families in which dystrophy of the facio-scapulo humeral type has prevailed.

Cardiovascular disease is rare. Two of the cases (161, 171) examined have rheumatic mitral disease, neither of them suffering from muscular disease. One myopathic (No. 118) at the age of 40 was suffering from hyperpiesia at the time when he was first examined, the systolic blood-pressure being 170 and the arterial walls correspondingly thickened; his kidneys also showed signs of sclerosis in 1923, and he died in 1931 of secondary heart failure.

Cataract, skeletal deformities, absence of muscles or muscle groups (in particular of the sternal portion of the pectoralis major), are not present in any member of the family who has been examined, nor is there evidence of any such deformities to be suspected in others unaffected by myopathy when direct examination was impossible.

No member of the family, as far as I can ascertain, ever married another descendant of Thomas S.

The size of the families has been about normal, considering their social position. Celibacy, sterility and unusually large families have occurred with about the normal degree of frequency, if we take into account the social status and the times in which they lived. The record of abortions is nebulous so far as former generations are concerned; there has been no unusual number in the last fifty years.

At birth, the babies have not been remarkable for their size—they have been neither big nor little. The usual rule has been that in

infancy and childhood the growth of myopathic members was either normal or slightly subnormal, but at puberty a rapid increase in weight has taken place which brought them to over-average dimensions in this respect. As young adults they are strong and have tended to excel at games involving muscular power rather than agility; most of those examined after the age of 20 have been in good general health, of good colour and exceptionally well covered with subcutaneous fat of normal distribution. Throughout their adult lives, the myopathic members of the family have a robust appearance; after the menopause, which occurs at the usual age, the affected women tend to put on fat to an abnormal extent. In old age considerable loss of tissue—both muscular and fatty—is evident in the only case available (46), who has shown signs of progressive myopathy for over thirty years. But even at this age there is no suggestion of a “living skeleton” about him, and he is mentally as alert as ever.

In a majority of affected cases there is a tendency for the legs to be short in proportion to the length of the body. This feature must have been much more marked in Case 1 than in those living cases whom we have observed, for in the latter the disproportion is of such small degree that it would not be likely to have given rise to the nickname “Ducky” by which Case 1 was known.

In height, no appreciable variation exists between myopathics and non-myopathics, all being of medium height with normal degrees of variation. No evidence of endocrine disturbance has been found other than adiposity. In particular, none of the cases show signs of dystrophia adiposo-genitalis, acromegaly or dwarfism, and no case of hyper- or hypo-thyroidism has been seen.

Such cases of other forms of neuro-muscular disease as have been found are few in number; they will be discussed later.

On account of the late onset of the disease and its slow progress in a majority of those affected, they have not been so far crippled as to be unable to earn a full living during the reproductive period of life; as a result an unusually large number of the myopathics have married, and have transmitted the disease to descendants.

THE MYOPATHY.

Perhaps the most interesting feature of this family group is the variation in the clinical picture at different stages. There can be no reasonable doubt that in all the cases the same fundamental inherited factor exists; yet a stranger to the family would probably classify one

case as a pseudo-hypertrophic paralysis, a second as the true Herculean type, a third as a distal type, and others as juvenile or transitional forms; one at least, on account of the myotonia of some of the muscles of the thigh, remotely resembles the myotonia congenita of Thomsen; whilst yet another was mistakenly diagnosed as a peroneal (neural) atrophy.

After examining many of the affected members of the family and learning their histories, I was forced to the conclusion that their varying forms represented, in the main, phases of the disease through which each member tends to pass. Nearly all of them are of heavy build, and the majority in their pre-myopathic state were of exceptional strength. In the only thin members affected (136, 209) there was no hypertrophic or pseudo-hypertrophic stage, progressive weakness with atrophy being the earliest features.

For convenience of description, four phases may be recognized—hypertrophic, pseudo-hypertrophic, atrophic and terminal. It need hardly be added that these stages merge into one another by a gradual process.

A.—The Hypertrophic Stage.

The first stage is that of true hypertrophy, and corresponds closely to that described by Spiller under the heading "*dystrophia musculorum hypertrophica vera*." I have selected two cases (Nos. 157 and 89), the first a girl, aged 9; the second, a man, aged 25; the former has been seen in this stage, and her description is direct. Case 89 was not seen by me until some ten years after the Herculean stage had reached its zenith, and is therefore an account based on the observation of others.

Case 157 is a girl, 9 years of age in 1923. Her outstanding physical feature is the magnificent development of the musculature throughout, but especially in the lower limbs. The joints are supple to the normal degree, but all movements are exceptionally powerful for the age of the child. This girl, though below the average age of her school class, was picked out as the central figure of a ballet on account of her finely-developed lower limbs and her exceptional capacity for toe-dancing. In height she is slightly above the average for age, but in weight and girth of limbs is much above the average of her compeers. Stance and gait, in walking or running, are perfectly normal. The muscles on palpation are firm like those of an athlete in training, but give no suggestion of toughness or fibrosis on handling. A discrimination at this early stage between the largeness of the muscles of the leg and those of the thigh leaves only a suggestion that the calf muscles are proportionately bigger than those of the quadriceps femoris group; for the latter are clearly above normal

size and power, though the presence of a good layer of subcutaneous fat makes accurate measurements impossible.

Both knee-jerks and Achilles-jerks are completely absent, even on Jendrassik reinforcement.

Her colour and general health are above average and the mental capacity well up to standard.

Case 89.—R. S., at 25, was a stockily-built man 5 ft. 9 in. in height and weighing 200 lb. He was unusually deep-chested, and his whole build suggested strength. Everywhere the muscles stood out in magnificent relief despite his goodly covering of subcutaneous fat. The calf muscles were large and firm, and the thigh muscles were on the same generous scale.

He stood erect, but not in any abnormal way. The muscles of the chest, shoulder-girdle and arms were finely moulded and of great size. They indicated correctly the great power of his arms in lifting and carrying. He was capable of lifting from the floor a 56 lb. weight between the thumb and finger of either hand. He could climb a flight of stairs with a load of 500 lb. on his back. About 1906 he attended a fair where a performing bear was wrestling with his keeper; in response to a challenge, he stepped forward, wrestled with the bear and laid it out! Realizing his great physical capacity, he became a furniture remover, and acquired both profit and pleasure in exhibiting his colossal lifting powers; but during the last twenty years the power of his legs has steadily diminished.

In the early years of his declining power the calves became larger than ever, and he often suffered pain in them on walking. So large did the left calf become that he was advised to consult a surgeon, and the latter came to the conclusion that a sub-aponeurotic lipoma was present. At the operation for its removal, nothing was found but a very large and fatty belly of the gastrocnemius muscle, of which unfortunately nothing was removed for section. Thereafter a rapid decline in power of his legs, progressive and still progressing, has occurred, and with it a steady diminution in calf measurement. Fig. 1 shows the appearance of this man in 1921, and figs. 2, 3 and 4 in 1931; they were taken in the third or atrophic stage.

B.—The Pseudo-Hypertrophic Stage.

The second stage marks the beginning of the decline in power.

Case 158.—A girl, aged 21 in 1923, is an example of this weakness. She is of unusual intellectual attainments, with very good general health and no suspicion of anæmia. Fully dressed she weighs 141 lb., and her height is 68 in. Her complaint is of an increasing difficulty in walking, noticed first after an attack of tonsillitis when she was 12 years old. The symptom to which attention was first drawn was a tendency to fall easily if her toe caught in any obstruction in bringing the foot forward in walking: to-day this is characteristically



FIG. 1.

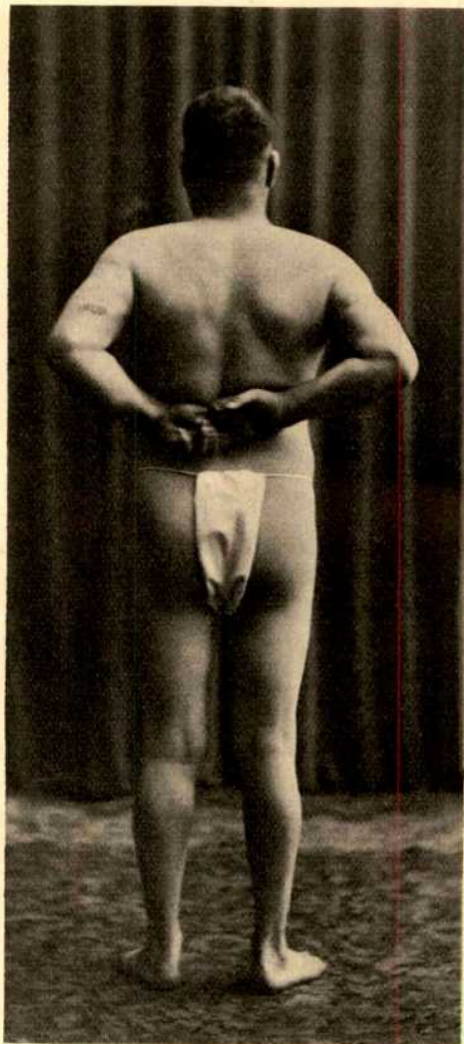


FIG. 2.

FIG. 1.—R. S. (Case 115). 1923. Aged 37. Early atrophic stage. Note the well-developed torso, moderate thigh muscles and poor leg muscles. No lordosis. There were no reflexes in the legs at this stage.

FIG. 2.—R. S. (Case 115). 1931. Aged 45. There has been only slight advance in muscular weakness and atrophy of the legs. The muscles of the shoulder-girdle are large.

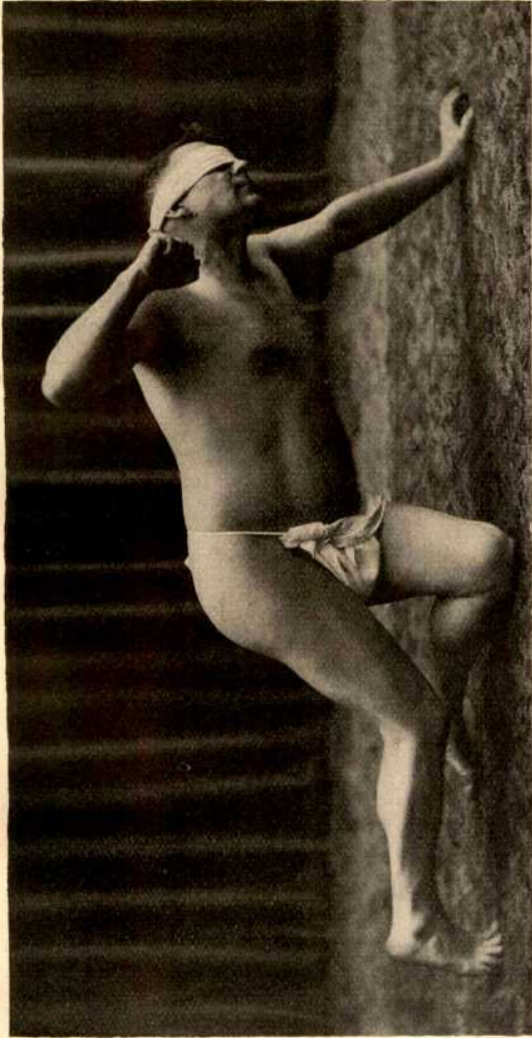


FIG. 3.

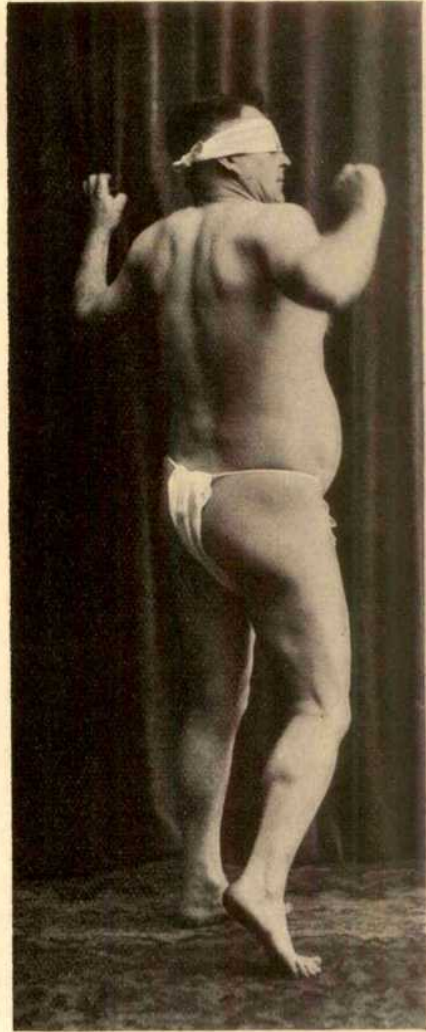


FIG. 4.

FIG. 3.—R. S. (*Case 115*). 1931. Aged 45. Lateral view. Increased adiposity.

FIG. 4.—T. S. (*Case 89*). 1931. Aged 57. A later stage of atrophy of the lower limbs. Much adiposity. Shoulder-girdle unaffected. No lordosis.

her worst symptom, as any slight irregularity of the ground which causes her toe to be held back a fraction of a second too long, results in a fall on to hands and knees.

The gait and stance in this patient would pass for normal except on close examination. Then it is found that in standing she is exceptionally upright, the knees being firmly locked in the fully but not abnormally extended position, the shoulders thrown well back and the chest and abdomen very slightly advanced. As she walks there is less than the normal forward inclination of the body at the hips, and each leg is swung forward loosely and with the foot a little higher than usual, until again the knee is locked in full extension; the heel is then brought sharply down to the ground and then the body weight is transferred to this limb by a jerky forward and lateral thrust of the other leg. The general effect is somewhat of a swagger of a loose-jointed kind; the family, who have lived with this gait in one or other of their relatives for years, call it the family "swank." As she walks on a stone pavement her relations can distinguish her gait at once by the sharp "clack" of each heel. She needs no artificial assistance and can walk a distance of two miles without undue fatigue, but beyond that limit is always conscious of an increasing ache in the calf muscles. She cannot run, and has not been able to do so since the age of 12 years. She can only pick up objects from the floor with great difficulty, unless she uses her free hand to help in sustaining the body weight whilst doing so. In getting up from the recumbent position, she "climbs up" herself in manner characteristic of cases of pseudo-hypertrophic paralysis. She is unable to stand without assistance if the knees are even slightly bent. All movements of the arms and trunk are of normal range and power, and there is no weakness in the muscles of the face or neck; speech, mastication, deglutition and closure of the eyes are all natural.

On physical examination the muscles as a whole are much above average size. In the upper extremity, power corresponds to size; in the lower, where the muscles are larger than would be expected in one of her build, they are much less powerful than would be expected. Owing to the goodly layer of subcutaneous fat, the muscles do not stand out prominently as in the usual cases of juvenile pseudo-hypertrophy, but their contour can be clearly defined during contraction on palpation. The calf muscles in particular are big, but their power is not much above half what would be expected of normal muscles of this size. The main weakness is in the extension of the knees, where power is barely a quarter of the normal; the flexors of the hips (ilio-psoas) have about half normal power. The tendon reflexes are absent throughout the lower limbs.

All the muscles of the upper extremities are fully normal, no wasting being present in the hands.

C.—The Atrophic Stage.

After passing through the pseudo-hypertrophic stage there is a gradual atrophy, with increasing weakness, in the muscles of the pelvic

girdle and in the lower extremities generally. At this period the cases show a sharp contrast between the flabby wasted muscles of the lower extremities and the powerful and well-developed muscles of the shoulder-girdles and arms. The only feature to which it is desirable to draw special attention is the fact that even late in this stage no muscle appears to be totally paralysed, though in some power is reduced to a mere fraction of the normal.

In one case (136) now living, the patient began her weakness with an atrophic process, there being no hypertrophic or pseudo-hypertrophic stage. It is noteworthy that this is the only case of fully developed dystrophy in this family in whom the bodily habit is (and always has been) thin. The distinctive features of this period, and in which the signs differ from those of the Charcot-Marie-Tooth type of peroneal atrophy, are:—

- (1) A tendency for the proximal muscles to be more affected than the peripheral, the psoas-iliacus being particularly weak.
- (2) A less complete loss of power in any individual muscle.
- (3) A more even degree of wasting of the whole lower extremity group, there being in particular no suggestion of a racquet-shaped bulge near the hip.
- (4) No sensory disturbance whatever. The tendon reflexes are absent in this stage, not merely in the atrophic lower extremities, but throughout the arms, in which size and power are still normal.

D.—The Terminal Stage with Distal Atrophy (Hands).

Case 46 is now 81 years of age. In his youth and early manhood he was of Herculean (true hypertrophic) build with the degree of adiposity characteristic of the affected members of the family. At the age of 30 he could carry a piano on his back, and could work at his trade as a furniture remover for twenty hours at a stretch; if a piece of string was tied round his upper arm he could snap it by contracting his biceps.

At the age of 50 he began to get painful cramps in his calves after exertion, and from this time forth became progressively weaker on his legs. By the age of 72 (when first examined) he had reached a stage at which walking was only just possible without a stick; the chief weakness was in the flexors of the hips, but all the muscle groups in both legs were of a power not more than 40 per cent. of the normal although no obvious loss of muscle tissue could be detected. At this stage there was noted for the first time a wasting in the intrinsic muscles of both hands; the first dorsal interosseous muscles were severely, and all the other small muscles slightly but definitely, wasted and weak.

At the age of 82, he has ceased to be able to walk without personal assistance, and there is widespread weakness, nowhere complete, in the muscles



FIG. 5.

FIG. 5.—T. S. (Case 89). 1931. Aged 57. Note the normal thenar muscles and pectorales.



FIG. 6.

FIG. 6.—T. S. (Case 89). 1931. Aged 57. The pectoralis major in contraction. Face normal.

A MYOPATHIC FAMILY

of both lower extremities. The lower half of each leg is involved in a gross oedema; the thigh muscles are now obviously wasted, and this is the more apparent as much of his adiposity has been lost. In the upper extremities, the atrophy of his hand muscles has advanced; weakness, and a degree of atrophy not quite commensurate with the weakness, is present in all the fore-arm and arm muscles, but is most marked in the flexors of the wrist and the long flexors of the fingers. The scapular group are only slightly weak and are not perceptibly atrophic. No tendon reflex can be elicited.

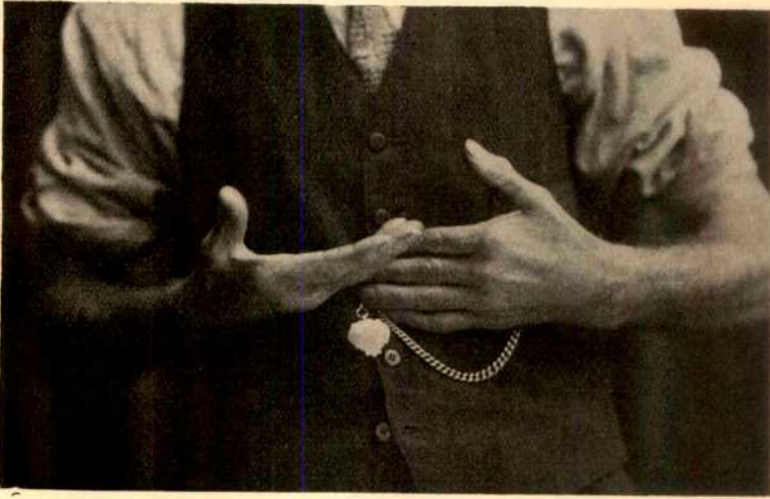


FIG. 7.—J. S. (Case 47). Aged 68. Atrophy of the radial interossei, but no *main en griffe*. The atrophy is typical of the terminal stage. This patient has no atrophy of the legs, but the tendon reflexes (knee and ankle) are deficient.

HISTOLOGY.

In only one case has it been possible to obtain material for section (Case 118). This patient was recognized as a myopathic member of this family in 1923, and was then found to have hyperpiesia and a hypertrophied heart. The blood pressure slowly increased and heart failure set in in the autumn of 1930. He died in February, 1931, at the age of 48. Dr. G. R. Bashford made a naked-eye examination of the body and removed certain fragments of muscles, no other examination being permitted. His report is as follows:—

"The body is in a fair state of nutrition. There is obvious wasting of the calves, thighs, gluteal and pectoral muscles out of proportion to that of the others. The first dorsal interosseous muscle in each hand is completely atrophied and the thenar and hypothenar eminences are slightly wasted.

"Measurements.—Calves, right 9 in., left 9 in.; thighs (6 in. above the

knees), right $13\frac{1}{2}$ in., left $13\frac{1}{2}$ in.; pectoral muscles, about 50 per cent.; gluteal muscles, markedly wasted.

"Portions of the gastrocnemii, soleus and adductor muscles of right thigh were taken for microscopical examination."

The portions of muscle removed were sent to Professor Haswell Wilson, who kindly prepared sections and the photomicrographs here produced, together with the following report:—

REPORT ON PORTIONS OF MUSCLE EXCISED POST MORTEM.

Sections, longitudinal and transverse, have been prepared from portions of the adductor magnus, gastrocnemius and soleus. Atrophic changes are present in each of these, but there is a marked difference in their intensity, being relatively slight in the adductor magnus and extreme in the soleus.

Adductor magnus.—In longitudinal section the muscle-fibres as a whole are attenuated in appearance. The cross striation is well preserved and there is but little increase in the interstitial fibrous tissue. Here and there, however, degenerated fibres are present. In these the sarcoplasm is swollen and glassy or granular in appearance; the striation has disappeared and in some cases the fibre is folded on itself within the sarcolemma. These changes are accompanied by proliferation of the sarcolemmar nuclei.

Gastrocnemius.—The changes are similar in nature but much more advanced. Practically all the muscle-fibres show degeneration, and striation is only occasionally visible. In most cases the fibres are granular or homogeneous in appearance. There is much proliferation of the sarcolemmar nuclei, and in places rows or clusters of nuclei indicate the remains of completely degenerated muscle-fibres. In some cases the fibres appear to shrink within the sarcolemma till they are no longer recognizable amongst the proliferated nuclei. In others the fibres become swollen and disintegrate. There is much new formation of delicate fibrillar connective tissue which separates the individual muscle-fibres, and with this there is some deposit of fat, though this is not extreme. There are many dense granular deposits of hæmatoxylin in degenerated sarcoplasm—evidently small areas of calcification.

Soleus.—No intact muscle-fibres are found in any of the sections, and only an occasional swollen cylinder indicates the remains of muscle substance. Its position is indicated by strands of hyaline fibrous tissue lying in fat. In this there are small collections of sarcolemmar nuclei or granules of calcification, but beyond this there is nothing to show the course of the muscle-fibres.

In some of the sections small medullated nerve-fibres are present. Though not stained by special methods it is obvious that these are degenerated. Many of the axis-cylinders have disappeared and the fibres have retracted within the nerve-sheath. The nuclei of the neurilemma have proliferated and there is some fibrosis of the nerve-bundles. There is no noteworthy change in the vessels.

The changes as a whole are those of progressive atrophy of the muscle-fibres, unaccompanied by any evidence of reaction except on the part of the

PLATE I.

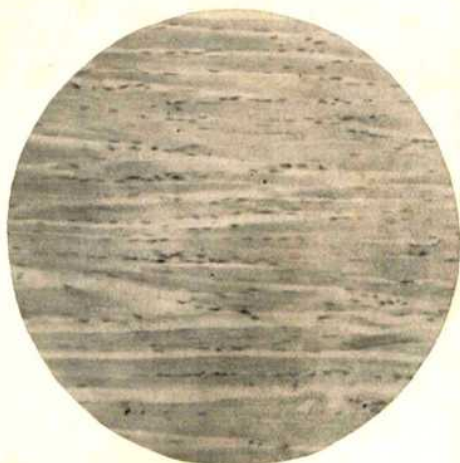


FIG. 8

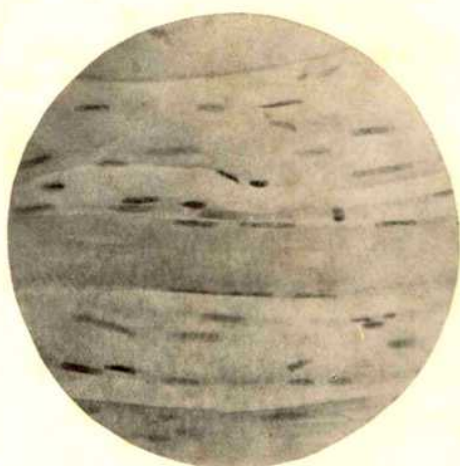


FIG. 9.

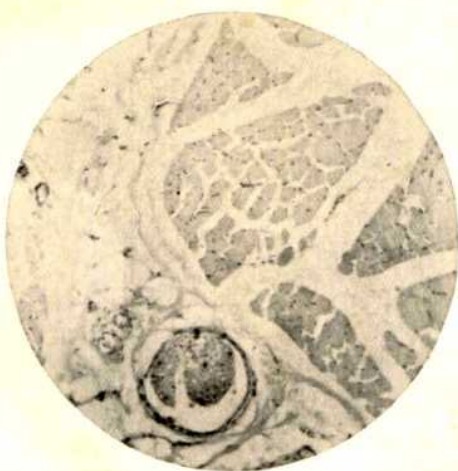


FIG. 10.



FIG 11.

FIG. 8.—Adductor magnus, longitudinal section. It shows the thinning of most of the muscle fibres and the proliferation of the sarcolemmar nuclei. $\times 100$.

FIG. 9.—Adductor magnus, longitudinal section. A single normal fibre crosses the centre of the field: in it the cross-striation is visible. On either side of it there are degenerate fibres with numerous sarcolemmar nuclei. $\times 250$.

FIG. 10.—Adductor magnus, cross section. The general shrinking of the muscle fibres is well shown. On one side of the section a small nerve is seen, which is retracted within its sheath; fibrosis with increase in nuclei can be distinguished. $\times 100$.

FIG. 11.—Gastrocnemius, longitudinal section. Swollen fibres cross the upper part of the field; rows of sarcolemmar nuclei are seen along their edges. Below the muscle is almost replaced by fibrous tissue, in which are a few sarcolemmar nuclei. There is a cluster of three irregular areas of calcification. $\times 100$.

To illustrate paper by Stanley Barnes.

PLATE II.

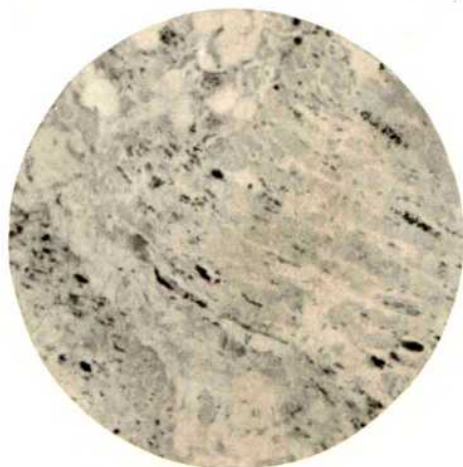


FIG. 12.

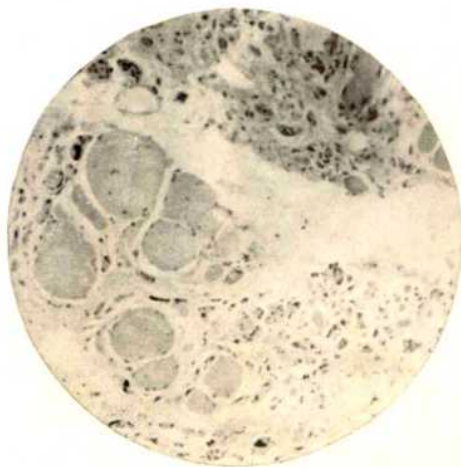


FIG. 13.



FIG. 14.

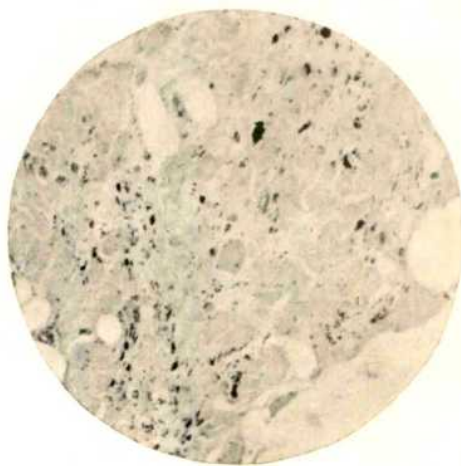


FIG. 15.

FIG. 12.—Gastrocnemius, longitudinal section. The section shows a more severely damaged part of the muscle. Dark hyaline fibrous tissue occupies the greater part of the field, with some fat and a few rows of sarcolemmar nuclei. $\times 100$.

FIG. 13.—Gastrocnemius, cross section. The section shows the contrast between swollen granular fibres and shrunken fibres marked out by sarcolemmar nuclei. $\times 100$.

FIG. 14.—Soleus, longitudinal section. This shows extreme degeneration. The muscle fibres are represented by strands of dense fibrous tissue in which a few sarcolemmar nuclei are just visible. There is considerable deposit of fat between the degenerated fibres. $\times 50$.

FIG. 15.—Soleus, cross section. A single swollen fibre is recognizable in the centre of the field. Elsewhere there is simply fibrous tissue with clusters of sarcolemmar nuclei and a small dark area of calcification. $\times 100$.

To illustrate paper by Stanley Barnes.

sarcolemmar nuclei. There is no evidence of phagocytosis and no lymphocytic infiltration. The degenerated fibres appear simply to shrivel, or to swell up and gradually disintegrate. Fibrous tissue proliferation and fat formation are such as may be found in any organ undergoing atrophy, and neither is present to an excessive degree.

DIAGNOSIS.

Although in the first instance there was some difficulty in determining the type of disease from which the patient was suffering, the examination of relatives who exhibited more advanced stages, together with the family history, soon left no doubt that the condition was a muscular dystrophy. The presence of pseudo-hypertrophy and absence of knee-jerks, the absence of all evidence of sensory defect or pyramidal disease, and the slow progress over long periods of time made no other diagnosis likely; the histological appearance of muscle sections confirmed the diagnosis. But the type of myopathy was unusual. The closest resemblance was to the pseudo-hypertrophic form; but from this it differed in that the inheritance was too direct, that the females were affected equally with males, and that the age onset was unusually (and nearly uniformly) much later than would be expected. Further, after the pseudo-hypertrophic stage the spread of the disease showed marked divergence from that type, for wherever the upper extremity was affected, the muscular weakness and atrophy were always of a distal type; it began in the intrinsic muscles of the hand, followed in the flexors of fingers and wrist, and only in the terminal stages affected the biceps, triceps and deltoid. Not only was lordosis never seen, but the sternal half of the pectoralis major, so frequently atrophied in the pseudo-hypertrophic form, has not been found deficient in any stage of any of these cases.

Similar contrasts separated out these cases from the Erb, Leyden-Moebius, Zimmerlin and Landouzy-Dejerine forms of the dystrophy. It is true that in the Herculean stage such cases as have exhibited this phenomenon conform very closely to the *dystrophia hypertrophica vera* of Spiller; whilst the type of upper extremity atrophy would compare with that seen in the distal forms described by Gowers, Batten, Spiller and others. But if we regard the clinical appearance as a whole, and not divorced from the course and progress of the disease, the cases in the S. family do not fully accord with any of the groups, and must be regarded as a variant, a special type of muscular dystrophy.

CLINICAL FEATURES.

Age at onset.—One of the unusual features of this family has been that on the average the age onset of the dystrophy has been very late. Although some have begun at a late juvenile period, a large majority have not manifested any clinical symptoms of myopathy until reaching the ages of 35 to 50. For instance, it was only after her daughter (158) had been found to be myopathic that Case 91, at the age of 45, first showed evidence of the disease. Incidentally, the occasional late onset makes our table of cases a little uncertain; some are known to have died early, and are believed to have shown no sign of the disease, although a son (118) of Case 55 suffered from myopathy.

Individual cases of late onset of myopathies of most forms abound in the literature, but this point was particularly stressed by Cottin and Naville. In their series of cases, which were chiefly isolated and not directly inherited, and which particularly tended to be of a peripheral distribution, the age onset ranged as late as 68, and in females particularly several cases were described which began after the age of 40.

All observers are agreed that the Landouzy-Dejerine type has, as a rule, a later onset and is slower in its course than the pseudo-hypertrophic dystrophy; many cases of the former survive to late adult age, whereas in the cases of the pseudo-hypertrophic form the usual rule is that five-sixths of the cases are dead before reaching the age of 21 (Gowers).

To a small extent the family shows a tendency to "anticipation" of its myopathy in recent members. As to how far this is really true is difficult to say. The fact is that I have seen the more recent cases and have therefore been able to make a diagnosis at an early stage, whereas in the older ones I have had to trust entirely to the history given by patients or their relatives—who naturally tend to give a later age onset than I might have found. Nevertheless, in a few cases recently seen (such as Case 158) the onset was obvious to the family at puberty, whereas the tendency in former years had been for manifestations to appear for the first time at 35 to 50. In former generations the onset of the disease was nearly always too late to be a bar to marriage; in a few of the more recent cases it is clear that the chance of parenthood has been greatly diminished. Thus the family group of cases here recorded, although in clinical distributions and general characteristics resembling the pseudo-hypertrophic and juvenile forms of myopathy most closely, yet in its tendency to late age onset resembles the Landouzy-Dejerine and the distal types.

Not only is the age onset late, but the progress of the disease is unusually slow. In most cases of myopathic disease the tendency is for the progress to be intermittent, and this tendency is exaggerated in the S. family. The Herculean stage has lasted in at least two observed members for fifteen to twenty years; the pseudo-hypertrophic, where the affected muscles are larger but weak, continues for about ten years in some cases and much longer in others, before a gradual decline in size brings them to the atrophic stage. At least two cases still alive have been suffering from weakness of certain muscle groups for thirty years, and are still capable of getting about and of doing useful work.

In many of the cases, the onset of the disease or a rapid decline in power has followed a trauma or some intercurrent affection. Case 158 began after an attack of tonsillitis; Case 89 went downhill rapidly after the operation on his calf for the removal of a supposed lipoma; and these examples could be repeated indefinitely. Similar observations are recorded (often in non-familial cases) by many authors, as, for instance, by Hoffman (after severe scalds); Bramwell (after being buried by a shell-burst, and in a second case after a severe strain of the back); by Spiller (after a fall from a scaffold); by Robinson (several cases after strain, pregnancy and intercurrent disease such as enteric fever or influenza). In view of the natural tendency of all who suffer from a disease to attribute it to some outstanding event in their lives and to regard themselves as intrinsically normal, I think it is possible that in all such cases the effect of the disease or accident is merely determinant, and that there is not yet produced sufficient evidence to show that any normally constituted person can, as a result of such accident, develop myopathy.

In general it may be said that, given the necessary underlying constitution, the age onset is brought forward and the pace of the disease process accelerated by malnutrition, by conditions of severe strain, and by accidents or intercurrent disease.

Another unusual clinical feature has been the absence of lordosis. No single case has shown this symptom, and although the relative adiposity of the family may have masked the presence of spinal curvature to some extent, it is certain that no striking abnormality in this direction has occurred. In the same way, contracture has been notably absent at any joint, perhaps because wherever a muscle has been materially damaged its corresponding antagonists have never remained intact. Only in a very late stage of the disease, as in Case 136, is this rule broken.

MYOTONIA.

As an isolated phenomenon may be mentioned the tendency to myotonic contraction in the thigh muscles of Case 117. Ever since he was in the hypertrophic stage he has noted that any over-exertion affecting his thighs, and especially in cold weather, would cause a more or less painful cramp in the vastus externus and rectus femoris of the right lower limb. This cramp would last for several seconds, and always tended to be present more after the muscles had been resting than after a little preliminary activity. No similar myotonic contraction was seen in him elsewhere, and in no other member of the family was any similar condition observed.

THE ABSENT KNEE-JERK.

The early loss of the tendon reflexes has been a notable feature in the cases here recorded. In many members of the family no other suggestion of muscular or nervous abnormality has been found. In many cases no tendon reflex (biceps, triceps, &c.) could be obtained in the arms, although these limbs had normal power and their muscles were not wasted. A noteworthy case (157) is a girl aged 9, who resembled the dystrophia musculorum hypertrophica vera of Spiller, with abnormally well-developed legs and unusual power in all movements, and who on account of her strength and agility elected to become a professional dancer; and she had no knee-jerks.

In some of our cases pains in the limbs after exercise, cramps, &c., have been a prominent feature; but in none of them has there been any perceptible objective change in sensibility or muscle-sense, other than the loss of vibration-sense recorded in the advanced stage of the disease in Case 46.

A comparison with other forms of disease causing weakness of the quadriceps femoris, and due to damage to the central or peripheral nervous system, shows that a fairly severe loss of power and muscle substance may occur whilst the knee-jerk is only proportionately diminished. In his paper on Thomsen's disease (myotonia congenita), Rosett mentions that he found on occasion the same absence of the tendon reflexes without any corresponding atrophy, whilst the myotatic irritability remained normal; and, as many of his patients suffered from muscular pains, suggested that "some nerve elements are involved in the disease."

Towards the end of his clinical career, that acute observer, Sir William Gowers, used to say that congenital absence of the knee-jerk

occurred in about 1 in 10,000 cases; that is to say, after an exhaustive examination in which he had been able to elicit no knee-jerk, he could find no neuro-muscular pathological condition which would explain the phenomenon. I know of no published figures on this subject, nor can I produce any figures of my own. In common with other neurologists, I have met with the same phenomenon on several occasions, and the impression I have received is that the frequency-rate is somewhat higher in the Midland area than the London experience of Gowers would suggest. Oppenheim regarded the Westphal sign in these cases as one of the stigmata of degeneration, and remarks that it is so exceedingly rare that in practice it need not be taken into consideration.

In our group of cases, the examination of "healthy" members was made with the object of eliciting any facts which might give a clue to dormant disease. For this reason it was found possible in the cases whose knee-jerks were absent, whilst the muscular condition otherwise appeared to be normal, to indicate the probability that the absent knee-jerk here depended upon the muscular abnormality.

Only a prolonged examination of the family records of such cases will determine whether the suggestion is correct that the Westphal sign in apparently healthy individuals is to be regarded as a "stigma of degeneration" in a general sense, or whether, as I believe to be the case in the S. family, it is evidence of latent disease of a specific type.

ADIPOSITY.

A characteristic feature of myopathic members of the family is a constant tendency to adiposity. With one certain and one possible exception, all the myopathic members have been heavily built in the early stages of the disease; not only are muscles and bones above average size, but the panniculus adiposus is always above average thickness. As the disease progresses beyond the pseudo-hypertrophic stage, the atrophy of muscle tends to be masked by a further increase in the fatty layer. In a few cases, the adiposity during the later stages of the disease has been of a gross type, weights of over 230 lb. having been recorded; but as a rule such cases as have lived beyond 70 years have shown a tendency during their senility to lose much of the added fat.

Apart from the adiposity and the tendency for all the myopathics to be of big general build, there has been a remarkable absence of any family tendency to skeletal or other defects. Thus abdominal herniæ, muscular asymmetry, absence of particular muscles, scoliosis, &c., have

not been noted; whilst signs of sexual or mental deterioration have been absent.

A large majority of the non-myopathic members of the S. family were definitely not adipose. Unfortunately, the case record does not in all cases state this fact, but a recent series of re-examinations of some thirty living relatives, and the observation of one of the most interested of the myopathic members (who has a comprehensive knowledge of the branch of the family derived from No. 5) confirms the opinion that all the "big" members become myopathic sooner or later. In no observed case has a non-myopathic member been found on examination to be adipose, though there is a record that Case 66 (who died 24 years ago) reached a weight of 280 lb. and lived to the age of 73 without becoming paralysed.

Of exceptions to this rule in adults there are one certain and one possible. Case 136 is a woman who is, and always has been, of slender build; weight about 110 lb. and height 61 in. Case 47 is a doubtful one; he has atrophy only of the interosseous hand muscles, and no other muscular weakness; he has always been lightly built, with a thin covering of fat. With these exceptions, all the myopathics are adipose, and all the non-myopathics appear to be normal in this respect. The adiposity tends in all cases to come on at about puberty, and is universal in its distribution. There is no case of dystrophia adiposo-genitalis in the whole of the examined cases; in fact all the evidence we can collect suggests that as regards fertility, the age of onset of puberty, and of the manifestations of secondary sexual characteristics, they are normal.

Signs of vegetative disturbance, such as cyanosis of the extremities, exophthalmos, myxoedema, &c., have been consistently absent, except (as in Case 46) where the paralysis has reached a high grade and the oedema and cyanosis of the feet may be regarded as a late effect secondary to the immobility, and to some extent dependent upon incipient heart failure.

Thus all the evidence we have collected from this family goes to show that the two conditions of myopathy and adiposity are present together, and that no other endocrine defects tend to occur with unusual frequency. Further, an adipose *forme fruste* comparable to the "Typ" of Diehl, Hansen and Ubisch, does not occur in the S. family.

As to whether the myopathy is secondary to the endocrine defect responsible for the adiposity, or as to whether both are dependent upon the same genetic factor, is a point which has been discussed by many authors (Diehl, &c., Robinson, Timme, &c.), who have already noted

this close association, and at this stage it would seem that no definite statement can be made. At the same time it should be noted that many myopathic patients do not exhibit adiposity; that some do not show any type of endocrine disturbance till long after the disease has developed; and that no satisfactory instance has yet been recorded in which dystrophia musculorum progressiva has arisen in the absence of a genetic defect of a myopathic character. On the whole, it is probable that the inherited defect responsible for the paralysis in our S. family is also causing the adiposity as a less important defect, for in some of the S. cases indications of myopathy (such as loss of knee-jerk) occurred first, and in most of these the adiposity manifested itself at a stage when the muscles were large and powerful. Such a conception of the mutant gene constituting the inherited morbid factor, is on all fours with observations recorded by the geneticists. As Morgan says (p. 304): "It must not be supposed . . . that mutant changes produce only single striking or even a single small change in one particular part of the body . . . Even in those cases where one part is especially modified, other effects are commonly present in several or in all parts of the body."

Abortive Forms, &c.

It has already been remarked that the family has been relatively free from other neuro-muscular diseases which must be regarded as endogenous. The myopathy has "bred true," and has not varied in its essential characteristics and course in any of the clearly defined cases. There are, however, a few cases of disease in the family which call for special notice. Case 177 (Emily S., aged 18) suffers from infantile hemiplegia and epilepsy; her father (Francis S.) has been examined and shows no sign of myopathy at the age of 56 and can now be presumed to be free from the inherited taint; there is thus a strong probability that the illness is in no way connected with the family disease. Case 188 was born deaf and dumb; his mother (of the S. family) at 47 is also free from any taint of myopathy. Case 123 was a boy born in 1882 who died when 5 years old, and of whom no record is available other than that of the parents; his father (Case 61) died in 1884 and was myopathic. This boy never walked; he was only able to shuffle along on his buttocks. He was an uncle of Case 177 and also to the family of Case 124, in which twelve out of thirteen children died before reaching the age of 10. There is thus a strong suggestion that some recessive factor has been introduced into this branch of the family, and

is partly or wholly responsible for the exhibition of disease. Case 168, belonging to a different branch of the family, is a Mongolian idiot. His mother is not myopathic, but two of her brothers and their father were so affected. It is again more likely to be due to some other recessive factor, inherited presumably from both father and mother, and independent of the myopathic taint, that the Mongolian condition arose.

Perhaps the most interesting member of this group is Case 47. Of the seven siblings derived from Case 12, five showed myopathy, one died childless at 50 and was free from disease, whilst their brother (Case 47) at the age of 68 has recently developed atrophy of the radial group of the intrinsic muscles of the hands. The atrophy is evenly bilateral, and does not correspond to that produced by pressure of cervical ribs; there are no signs that progressive muscular atrophy of a spinal type is developing; careful examination has excluded all the ordinary causes of such atrophy. I am inclined to the conclusion that in this case we are dealing with an undeveloped form of the disease in which hand atrophy is preceding pelvic girdle weakness, and in which the disease factor has lain dormant for an unusually long time. This view is supported to some extent by the fact that the ankle-jerks were absent even on reinforcement, although the legs showed no sign of weakness. The variation in the character of the disease in this case is all the more noteworthy in that (with one exception, Case 136) he is the only affected case seen in late middle life in whom the bodily habit has been slender. All of his children, none of them being yet 45 years of age, are so far free from myopathy.

It thus appears that, in this family, aberrant forms of the disease, if they exist at all, are exceedingly rare, and that if the disease exhibits itself in any way it is apt to progress in the same orderly fashion in all members of the family.

These results correspond fairly closely to other observations made on families when the disease has been transmitted in the dominant mode, but differs materially from what has been found in other groups. Notably is this so when isolated or small numbers of cases only have occurred in family groups. Davidenkow and Kryschowa (1930) found many conditions, especially in the mothers and relatives of myopathics, in whom no true dystrophy was present but in whom neuro-muscular anomalies existed which in their opinion were indications of an underlying defect; included in this list were ptosis, big calves, deformities of the sternum, imperfections of the abdominal muscles leading to hernia, and anomalies of the vegetative system. In the cases of Diehl, &c., no

such variety of defects occurred; but a single well-defined type (adipose, stunted growth, sloping shoulders, &c.) was frequently seen and appeared with such regularity that they formulated the theory that in their myopathic cases the mode of inheritance was a double (dimeric) dominant, and that the adipose types were those members of the family who carried one only of the factors necessary to the manifestation of myopathy. In relatives of Minkowski and Sidler's cases, arising as an explosive outbreak similar to that which has been noted in myotonia atrophica by Fleischer, there were found no cases of idiocy, stunted growth, &c. The most notable general feature of their family group was the very high infantile mortality in the generation to which the patients belonged as compared with that of their parents.

Many records of individual cases are available in the literature where arrested forms of myopathy are believed to have been met with (Bramwell, Marina, &c.), that is, a non-progressive muscular weakness existed in cases where no other diagnosis could be accepted. It is probable that in some of these the disease was true myopathy of late onset and of very slow development, comparable, for instance, to what has been found in our S. family in Case 46 at the age of 50, or in Case 157 at the age of 10. Unfortunately in a large series of the older records no observations are reported of the physical condition of ancestors and their collaterals, which might have brought to light forms of aberrant defects suggesting a defective family trait, not frankly myopathic. It is of great importance that, in dominantly as well as recessively-transmitted cases, such records should be brought together in order that a judgment might be formed as to how far the various kinds of *formes frustes* are fortuitous, and how far they are to be regarded as phases of an underlying myopathic basis, not exhibiting true myopathy, either because of the absence of some other factor, or because other constituents of the genotype are able to hold in check the manifestation of muscular dystrophy.

For the moment the various *formes frustes* which have been described may be divided into two classes. The first will include all cases in which there are present features typical of myopathy, such as exceptionally big calves, absence of the sternal portion of the pectoralis major, partial defects of various muscles (especially the orbicularis palpebrarum) and perhaps congenital absence of tendon reflexes. These defects are specific, in the sense that they form features of various forms of myopathy, and may be either cases of arrest or of long-continued stabilization. The second group of *formes frustes*, less generally accepted and still requiring further investigation, consists of a series of physical defects

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of a less specific type, in that they are not persistently present at any stage in myopathics; these defects include adiposity, stunted growth, gigantism, acromegaly, and other indications of endocrine damage or imbalance of congenital origin.

POLYMORPHISM.

Such polymorphism as is seen is often more apparent than real. In the S. family there have been seen at varying phases forms which from the distribution of the damage and the size of the muscles might be classified as either hypertrophic, pseudo-hypertrophic, juvenile, and even distal; but a careful analysis of the histories shows that such polymorphism is here dependent upon the stage of the disease at which the observation is made, and that all of the cases tend to pass through these four phases. It is true that in several members, and particularly in Case 136, the only myopathic of the group who was thin, there is no record of a hypertrophic or pseudo-hypertrophic stage; the disease here began with atrophic weakness in the legs. Similar observations by other authors (Schultz, Keferstein, Weitz, &c.) suggest that we should regard pseudo-hypertrophy as a characteristic but non-essential element of the disease, which will occur in certain types of myopathy provided that its exhibition is not prevented by endogenous or exogenous factors which are independent of the specific factor causing myopathy.

In a few cases in the literature there have occurred diverse types of myopathy in particular families. Weitz, in his careful review, collected a series of such cases together, and compared them with his own and other groups. Briefly the conclusion at which he arrived, and which the record of the S. family supports, is that there is a constant tendency for the cases in each family group, and especially for those directly inherited, to appear in the same form and at the same age. The rule is often broken in the case of age onset, and this is to be attributed partly to endogenous factors involving genes other than the mutant responsible for the myopathy, and partly to exogenous conditions such as defective nutrition, strains and intercurrent disease. The development or absence of pseudo-hypertrophy would appear similarly to vary greatly in such groups, and is also probably conditioned largely in the same way by both endogenous and exogenous factors. In a few cases, as for instance those of Schumacher where one case of twins was of the Landouzy-Dejerine type and the other pseudo-hypertrophic, it is possible that the mixing of the types was due to two different strains of myopathy being inherited, a condition which must be as rare as is the

solitary observation. From the point of view of its genetics, the facio-scapulo-humeral form stands out almost, but not quite, as a separate entity; whilst the other forms—pseudo-hypertrophic, juvenile, hypertrophic, &c.—though tending constantly to appear in the same form in other members of the same family, will show considerable variations in age onset, in distribution of the muscle atrophy, and in the presence or absence of pseudo-hypertrophy.

The distal form (Oppenheim, Gowers, Batten, Spiller) is so rare, and such a small number of family groups have been recorded, that little can be said of its genetics. It seems certain that it exists as an entity, and is distinct from the Charcot-Marie-Tooth form of peroneal atrophy. In our own group, Case 136 at one stage (in 1916) showed signs so closely resembling the neural type that a mistake in diagnosis assigned it to the latter group, the atrophy being present in distal form, slightly in the upper extremities and widespread (though mainly peripheral) in the lower. It was only when this case was known to be associated with the family, and it had been found that all the S. cases in a late stage developed atrophy in the intrinsic muscles of the hands, that the diagnosis could be corrected. Atrophy of this type commencing in the hand muscles is evidently very rare except in the true distal form, and occasionally as a *forme fruste*. I have been able to find no record of another case in which such a distal atrophy began in the upper limbs when the myopathy in the lower ones was mainly proximal. In this connection it is interesting to remember the family recorded by Thompson, who found that over five generations seven individuals out of sixty-four developed atrophy of the hands comparable with that in the S. family, but without any other sign of either myopathy or neural atrophy; the author was of opinion that in his cases the atrophy was secondary to cervical ribs, and that the latter had been the primary inherited factor.

Thus, so far as the dominant families of myopathy are concerned, it is rare to meet polymorphism if that term is used to indicate essentially different types of the disease; but it is common to find types which have a superficial difference from the expected form, but which in reality are only phases in the course of a long-drawn-out and kaleidoscopic clinical picture.

INHERITANCE.

The conclusions which Mendel reached as a result of his investigation into the results of breeding in plants have been subjected to all manner of tests in many different species, and are accepted to-day

fundamentally unaltered. "The theory postulates the existence of a number of individual particles of substance in the germ-plasm each of which controls the development of some particular tissue or character in the developing organism. It demands that in respect of any particular character the individual must receive from its parents, one from each, through the gametes, two factors, either similar or dissimilar,

Case No.		Affected		Not affected		Totals		
Sex (Parent)		M.	F.	M	F.	M.	F.	M. and F.
M.	1	2	—	2	—	4	—	4
M.	5	2	3	—	1	2	4	6
F.	10	—	—	—	1	—	1	1
F.	11	1	—	2	2	3	2	5
M.	12	3	3	1	—	4	3	7
M.	15	5	3	—	1	5	4	9
M.	46	1	1	—	3	1	4	5
F.	49	—	—	—	2	—	2	2
F.	50	1	—	2	2	3	2	5
F.	51	—	—	1	3	1	3	4
M.	52	2	—	—	3	2	3	5
M.	60	—	—	2	—	2	—	2
M.	61	—	—	2	3	2	3	5
M.	68	—	—	1	2	1	2	3
F.	64	1	1	2	1	3	2	5
M.	65	—	1	4	—	4	1	5
F.	67	—	—	3	1	3	1	4
M.	89	1	1	—	—	1	1	2
F.	91	1	1	1	—	2	1	3
M.	115	—	1	2	3	2	4	6
M.	117	1	1	3	3	4	4	8
M.	131	1	1	7	3	8	4	12
14 M. } 22 8 F. }		22	17	85	34	57	51	108
		39		69		108		

according to whether or not in respect of this character the parents were alike or different. . . . It postulates that the association of dissimilar factors within the zygote is not attended by any adulteration effect upon them" (Crew).

In recent years the wide range of experiments carried out by modern geneticists has confirmed the theory and has enabled them to build up a new science. As to how far their results agree with the observed facts of human inheritance must be of absorbing interest to neurologists, and I propose to investigate the records of the S. family, and other published myopathic family groups, to determine whether in the first place the modes of inheritance can be so interpreted on Mendelian lines as to lead us to suppose that in all cases the inherited factor is a *sine qua non*; and, secondly, to determine if possible whether all the differing clinical types of myopathy are dependent upon an identical causal factor.

Mendel's second law—the law of segregation and of independent assortment—requires that if inheritance is in the dominant form, not only shall some of the first filial generation show evidences of the special character, but that the members of that family so affected shall be roughly one half. Seeing that the assortment of factors in the gametes takes place at random, it may easily happen that when members are small, as in the members of a human family, wide variation in the percentage may occur; but wherever a considerable number of cases can be brought together, the fifty-fifty ratio should be approached. Further, it will follow that in cases in which the inheritance is of a pure dominant type, no member of the later descendants of the family should show signs of the variant factor unless one of his parents also exhibited it.

PARENTS myopathic	CASES AFFECTED IN FAMILY GROUPS.		
	Sons	Daughters	
Males			
14	18	15	Affected
	24	22	Unaffected
Females			
8	4	2	Affected
	11	14	Unaffected
Percentages	Males	Sons affected	43 per cent.
		Daughters affected	41 "
	Females	Sons affected	27 "
		Daughters affected	14 "

Analysing our family group for this purpose, we find that in each generation (P_1 the parental, to F_5 the fifth filial) the disease has appeared. Further, of those myopathics who married and had families, but excluding as doubtful Case 47, and including as myopathics all who had absence of knee-jerks, we find that in 22 families in which either father or mother was myopathic (and where the other parent was presumably free from the taint), there were 108 children in all, the myopathics being 39 and normals 69, the percentage of the children showing myopathy was thus 38. In the 14 families where the affected parent was the father, 18 sons were affected out of 42, and 15 daughters out of 37; in the 8 families where the mother was the affected parent, 4 sons out of 15 and 2 daughters out of 14.

Setting out the totals in a different way, we may say that in cases where the affected parent was a male, 43 per cent. of sons and 41 per cent. of daughters were affected; where the mother was affected, only 27 per cent. of sons and 14 per cent. of daughters showed myopathy.

Admitting that the figures are too small for any final conclusion, yet they are large enough to be significant, and to indicate that some special factor is operating if Mendel's law is being followed. Probably the most important factor is an inherent defect in the genealogical table if it is taken at its face value. Just as the older section of the family tree may be imperfect in that it depends upon the memories and records of descendants, and that the cases dying before 1921 have not been personally examined, so the most recent section is vitiated by reason of the youth of many of the persons indicated. It has already been observed that many cases have shown no sign of the disease obvious to relatives until well on in middle life, and in some cases not till 60 years has been reached; and although a medical examination may have shown the first elements of the myopathy at an earlier stage, yet no case could be certified as free from the possibility of future disease until at least the age of 45 was reached. Case 46, though now suffering from an advanced stage of myopathy at the age of 81, only began to be obviously affected at 50. Significant also in Case 118, whose parents were both believed to be free from the disease, though he suffered from it; this unique departure from the family rule of inheritance can only be attributed to his mother having died at the early age of 30, and before she had reached the age at which the disease is usually manifested in this family. When this patient first came under my notice, it was the unusual character of his myopathy and its correspondence to that of the S. family which enabled me to direct his attention to the relation-

ship to the S. family; a fact of which he had not been aware previously.

Any attempt to eliminate from our case list all families in whom the children of myopathics have not yet reached the age of 60, involves us in making a record largely on unobserved cases, and is probably less trustworthy than the inferences to be drawn from the list as it stands. But if we allow for the presumption that some at least of the younger "unaffected" cases will develop the disease in later years, the figures will approach the fifty-fifty ratio.

To sum up: in the S. family the disease has been transmitted by males and females, who have been affected in about equal numbers; it has appeared in each generation, and has never appeared in any descendant of Case 1, whose parent did not exhibit the disease, with the one exception where the early death of a potentially affected parent prevented the exhibition of the myopathy. Finally, the ratio of affected to unaffected children is substantially what would be expected in inheritance of a dominant type.

OTHER MYOPATHIC FAMILIES.

A considerable number of myopathic family groups are now to be found in the literature. Unfortunately, in most of them the numbers are small, and it has not been possible to trace back evidence of the disease through more than a very small number of generations, and in some no examination of relatives reputed to be normal has been possible on such a scale as is necessary for any final conclusion to be drawn as to whether the disease was inherited. In some groups, however, many details are available, and it is interesting to determine how far the forms of inheritance which are brought forward or can be deduced correspond to those in the S. family.

Robinson collected a number of cases all occurring in one family, and all being of one type. In the course of the five generations through which the disease was traced, the family had scattered somewhat widely through different States, but he was able to collect records of 128 children of affected parents. Of these, there were affected 82 (or 64 per cent.), the proportion of boys affected being 65 per cent., and of girls 63 per cent. The myopathy affected the shoulder-girdle group of muscles almost exclusively, neither face nor lower extremities being damaged; the regular age of onset was puberty, and a little earlier in girls than in boys. In this group the inheritance was clearly of the dominant type.

Weitz, in 1921, recorded a series of cases of his own, and analysed in addition all those in the literature where sufficient facts had been given from which conclusions could be drawn. He found that of familial cases (35 families) there were 94 affected (72 males and 22 females), and 101 healthy (43 males and 58 females). He noted also that in the directly inherited cases the disease tends to assume a less severe form than in the sporadic or isolated ones. In the former type also, he notes that variations of a minor character only occur in a family, and that although the age-onset tends to be the same in each generation, this rule is often broken; anticipation at an earlier age in later generations was not the rule in most cases. He came to the final conclusion that the inheritance takes place either in the dominant, simple recessive or sex-linked recessive form, and that many cases must be explained on the supposition that new mutations have arisen.

Niwa, in a short record of three dystrophic families, found that the transmission was direct through males and females in the Landouzy-Dejerine type, and indirect (sex-linked recessive) in the pseudo-hypertrophic. He made the interesting observation that blood grouping is not necessarily linked in inheritance with the myopathy, though there is a tendency for this to happen.

There seems to be general agreement that the facio-scapulo-humeral type of myopathy is nearly always directly inherited (Niwa, Davidenkow and Kryschowa, Eulenberg and Cohn, and others). On the other hand, the neural atrophy of the Charcot-Marie-Tooth type was investigated from the point of view of inheritance by L. de Lisi, and he came to the conclusion that the disease is transmitted in all forms—dominant, simple recessive and sex-linked recessive.

An important piece of research work on a large myopathic family is published by Diehl, Hansen and V. Ubisch (1927). They recall that Weitz in his monumental work in 1921 collected together and analysed from the point of view of inheritance no fewer than 639 cases of the disease, and came to the conclusion that of these 62·4 per cent. were isolated cases; that in family groups about 50 per cent. of children were affected; that of all cases the proportion of males to females was 476 to 163; and that the malady was often transmitted by a healthy mother. They agree that if the ordinary dominant form of inheritance obtains, the only way in which to explain the occurrence of the isolated cases is on the assumption of the origin of a new mutation. They then analysed their own large family of cases and examined each member—myopathic or not—with great care, not merely for signs of muscular

defect, but for evidence of other structural departure from the normal. They discovered that the family could be divided up into three groups—healthy, "Typ" and myopathic. The "Typ" cases had peculiarities of form common to one another but differing from the normal. They were small, thick-set and fat, with badly-modelled shoulders sloping in such a way that the breast appeared to be sunken. The other groups contained myopathics on the one hand, and "healthy" cases on the other. The latter as a rule were tall, thin and bony, with a straighter stance and good shoulder contour.

The genealogical table was then set out to show the three forms of cases—healthy, "Typ" and myopathic. They found that of 6 affected parents, each with a presumably normal mate, there were 34 children—16 healthy, 8 "Typ," and 10 suffering from myopathy. Postulating two factors (C and D), not linked but each derived from a separate parent, the expected result should have been 17, 8.5, 8.5, a correspondence so close as to confirm the postulate. From this and other considerations they came to the conclusion that in their family two separate mutants, C and D, must be present to give rise to a case of myopathy; and that the "Typ" was due to the presence of one such mutant, D. Thus their healthy cases might be of the genotype $ccdd$ or $Ccdd$ or even $CCdd$, whilst the "Typ" cases were those in whom D always appeared without the special factor C, their genotype being $ccDd$ or possibly $ccDD$. If an apparently normal genotype who carried the C factor mated with a "Typ," myopathy could occur in the next generation in that a proportion of the F₁ group would be represented by the formula $CcDd$; the presence of both C and D in one genotype determining myopathy.

Diehl and his collaborators gave many reasons for thinking that the preponderance of cases in which males are affected and who derive this disease from a healthy mother, is artificial. They point out that for psychological reasons the existence of the defect is apt to be suppressed in the female, and that such disability as they may suffer may be no effective bar to house work, whilst the males all tend to come to light either at examinations for military service, or for failure in industry. Further, the tendency to suppression in the female results in a much larger number of myopathic females marrying than is the case in males. On this and other grounds they see no reason for believing that a sex-linked inheritance need be postulated.

It is noteworthy that in the allied condition of myotonia atrophica a form of inheritance had already been described by Fleischer which is

very similar to that put forward by Diehl and his collaborators. Fleischer found that in generations previous to that in which the explosive outburst of myotonia atrophica occurred, there were no cases of the fully developed disease; but that many and various evidences could be elicited of structural defects which could only be attributed to the inheritance of morbid factors. These defects were pre-senile cataract, failure of closure of the eyes during sleep and imperfect development of certain muscles.

Minkowski and Sidler (1928) investigated all the cases of myopathy they could find arising in a population of 1,700 in a Swiss village. The village was to a large extent self-contained and the inhabitants rarely married outside their own community, so that a considerable degree of consanguinity existed between the various members.

There were no cases of idiocy, stunted growth, etc. In the case of the dystrophic families (10 families containing 13 cases of dystrophy), 10 pairs of parents had had 68 children, of whom 32 died in infancy; whilst in the earlier generation, when consanguinity was of still higher degree, only 26 out of 127 children died in infancy. Some cause other than mere consanguinity must therefore be causing this lack of viability, and similarly must be a cause of the muscular dystrophy. Although they found no case of myopathy in the direct ascendants of the affected cases, a careful inquiry revealed that in all cases each parent was a descendant of each of two particular family groups living in the sixteenth century. The explosive outbreak of the dystrophy could not be explained by the fact of consanguinity, which was closer in the previous generation; but it could be explained on the basis that the genotype of each parent contained a recessive factor derived from each of the stems R and H in heterozygous form; whilst the myopathic children were homozygous in respect of both recessive factors. They therefore concluded that the mode of inheritance was a Double Mendelian Recessive, and that the mutations giving rise to the disease probably occurred in the sixteenth century. There was no evidence of sex linkage in their cases; *formes frustes* and defects in the skeleton or musculature of relatives, do not appear to have been present.

Davidenkow and Kryschowa investigated the mode of inheritance, especially in a series of cases of the Leyden-Moebius type. They noted the frequency with which the collaterals of the mothers were affected and confirmed the earlier observation that a myopathic man may have a healthy daughter who herself may have a myopathic son. They looked for and found in many instances cases of skeletal or muscular defects in

relatives, such as herniæ, imperfections in the abdominal wall, sternum or vertebral column, ptosis and anomalies of the vegetative system.

Their general conclusion was that the disease is essentially dominant in its form of inheritance, and that the structural defects noted in the earlier generations, and particularly in the mothers and their siblings, were latent or abortive indications of the presence of the underlying genetic factor. These *formes frustes* were not specific for myopathy, many of them being defects not generally occurring in typical cases. They concluded that the same genetic factor could give rise to differing forms of neuro-muscular and skeletal defects in different individual members of the same family groups.

At this stage, and with so few adequate records of myopathies available, it is hardly possible to arrive at a final conclusion as to the mode of inheritance. Generally speaking, the numbers in each group are too small for the arithmetical methods of the geneticists to be applied with any degree of certainty, and the observations so far recorded are too discordant. Probably a clearer approach to the subject could be made if we separate out the groups of cases. Putting by themselves those families where the developed disease has occurred in each of several generations, and in which the inheritance is clearly of a dominant character, we find that they show certain characteristics in which they differ widely from the other groups; they tend to breed true to type, and are polymorphic only to a small degree; they tend to occur in females with a frequency only slightly differing from that in males and to arise at the same period of life (homochronia); they are only moderately disabling in their manifestation; and *formes frustes* are rare. This group of the myopathies will include most of the cases of the Landouzy-Dejerine type, and a few of each of the others (pseudo-hypertrophic, juvenile, Leyden-Moebius, Zimmerlin, and variants). On the other hand, the "isolated" cases, and those which occur in small numbers and often in one generation only, although they exhibit the same structural damage in the muscles, and often correspond closely to the forms of the other group in the regional distribution of the damage, tend to affect males far more frequently than females, to manifest themselves at all ages, are much more disabling in their intensity, and are associated with many evidences in their relatives of polymorphism, both of true myopathy and of abortive forms (*formes frustes*).

The careful work of Diehl, Hansen and Ubisch, and the equally painstaking records of Minkowski and Sidler, leave little room for doubt

that in their cases the disease factor was inherited in double form, and that it was the co-existence of two mutant genes in the genotype that gave rise to the myopathy. But it is clear that though each group of authors puts forward a form of inheritance postulating two factors, whose co-existence in a genotype is necessary for the manifestation of myopathy, the modes of inheritance suggested are not identical; in the former a double (dimeric) dominant is deduced, the corresponding chromosomes not being homologous; in the latter, a homozygous genotype is propounded, in which each of the pair of chromosomes carries both factors (i.e., a double recessive form of transmission).

At present it would appear that the varying forms of myopathy are not transmitted after any single mode, nor does it appear necessary to assume that the same mode of transmission shall be present if the disease is one *sui generis*. Dominance is a relative term, and all kinds of variations in its degree occur. In our own cases, and in a large majority of those published, the dominance only becomes manifest late in life, so late that it must have been wrongly regarded as recessive in our Case 118, had that one been examined as an "isolated" one. The degree of dominance of a mutant must to some extent be determined by the other thousands of genes present in the zygote in order that we may explain the heterochronia, whilst the rarity with which true polymorphism occurs in the larger family groups suggests strongly that it is in them always an identical mutation of the same gene, but that in other groups mutations, possibly allelomorphic, are responsible. As to whether a second specific mutant factor is present in all cases (so that a "combined action" is necessary to manifest myopathy) is a point that can only be cleared up by further research in the same careful way as that pursued by modern workers. In our own cases it is clear that if two factors are present they are linked together in the same chromosome, though Cases 66 and 136 suggest the possibility that the factor for myopathy has been lost in the one and for adiposity in the other.

In general the position may be summed up as follows:—

- (1) In some cases one mutant only need be postulated.
- (2) That the mutation is not always identical.
- (3) That in some cases the mutant gene is so completely dominant that its presence is expressed in every genotype which carries it, whilst in other cases the mutation is fully recessive, and is only manifested in genotypes carrying the mutant in each of two paired chromosomes.
- (4) The preponderance of the affection in males in the second group of cases (i.e., those whose inheritance is not clearly of a dominant type)

is so great that it is not yet possible to exclude the possibility that the mutant is sex-linked (i.e., has its locus in the X or female sex-chromosome).

(5) In some groups of cases the presence of two mutant but non-allelomorphic genes provides the best explanation of the origin of the disease, and this may occur either in homozygous or heterozygous form (CC DD or Cc Dd).

(6) New mutations may arise; such a primary change in the zygote is probably a rare manifestation, and does not account for more than a small number of the cases recorded.

CONCLUSION.

(a) *Clinical.* (S. Family.)

(1) A variant of myopathy, occurring in many members of a single family, is here described which passes through four phases: hypertrophic, pseudo-hypertrophic, atrophic and terminal, the last stage being associated with a distal atrophy of the upper extremities.

(2) Other clinical characteristics are early loss of tendon reflexes, late onset and slow progress; an almost constant association with adipositas universalis, and a relative absence of *formes frustes* and of polymorphism.

(b) *Inheritance.* (General.)

(1) A large and increasing body of evidence is available, which goes to prove that myopathy (muscular dystrophy) is determined at the birth of the ovum, and is derived as a factor or as factors inherited from one or both of the two gametes which form the zygote. In rare cases, a new mutation (variation in a normal gene) may arise and be the cause of the condition in the individual developed from that zygote, and be transmitted to his descendants.

(2) As to whether the effects of the mutant are manifested directly during the development of the individual, or indirectly through the endocrine glands, has not been established. The frequent association of myopathy with adiposity and other evidence of endocrine imbalance, may be interpreted on strictly genetic lines, the hormone disturbance being a secondary effect of the mutant.

(3) In those cases where microbic disease, trauma, overwork, etc., are antecedent in the history, they are merely factors which determine the onset or accelerate the progress of the disease in an individual who is a potential myopathic, i.e., a genotype carrying the mutant gene or

genes. Apart from the presence of such underlying factors, it is probable that the muscular dystrophy can never arise.

THE FAMILY RECORD.

The records given here are culled from various sources. Many—all the earlier ones—are abbreviated from notes supplied by older members of the family still living. The family name for the disease has been, not unnaturally, locomotor ataxia.

Where atrophy has been mentioned either as being present or absent in these notes, a reservation must be made on account of the goodly covering of panniculus adiposus which may to some extent mask diminution of size in the muscles, and which is so abundantly present in most affected members of the family. This reservation does not, of course, apply to atrophy of the intrinsic muscles of the hands. In Case 46, gross oedema of the feet and legs masks (1931) a possible atrophy of the tarsal interosseous muscles.

A few living members have been examined many times, but most of them have been examined once or twice only. In all, about 160 descendants of Case 1 have been examined. The first occasion was in 1922, when I had the assistance of Dr. E. Weston Hurst; the last was during 1931, when Dr. G. R. Bashford and Dr. E. J. Kerr helped me to continue the record.

In the main, for brevity, only positive findings are recorded. In all cases where tests were made, electrical reactions were of normal (not R.D.) type. In no case was any loss of size or power detected in the sternal half of the pectoralis major muscles, in the face or sternomastoids; the eye muscles and bulbar groups have been consistently normal. In no case was fibrillation seen, but the heavy layer of fat covering most of the affected muscles would have made it difficult to observe it, even if present.

In a few cases details are given of the size (by limb circumference) and power of muscles. The latter was estimated by putting the patient's muscles into active contraction against resistance by the observer, and a rough estimate was thus formed as to the power remaining; no accuracy in detail is claimed for the figures given.

At the time the earlier of these examinations were chiefly made, I was not aware of the observations of Diehl and his collaborators, so that the records of adiposity in other (non-myopathic) members of the family are imperfect. My recollection is that in those I have seen personally (about seventy in all) adiposity of abnormal degree is absent.

CASES.

1.—*Thomas S.*: Migrated from Leicester to Birmingham in 1776, where he founded a very successful business. Believed to have been born in 1749, and is known to have died in 1836. His will, made in 1835, mentions 11 children (8 sons and 3 daughters); in respect of 7 of them, it is not known whether or not they were myopathic, and they are omitted from the table.

Thomas S. was nicknamed "Ducky" on account of his gait. Was of powerful physique, had a long body and short legs. Had difficulty in getting about during his later years, and a specially constructed buggy was built for him with a very low step, so that he could haul himself into it. He had increasing paralysis of the legs up to the time of his death.

2.—*William S.* (son of Case 1): Born 1797, died 1871. Said to have been "shaky" for a few years before death, but was probably not myopathic. A photograph (about 1865) shows no atrophy of his hands. Was tall and well built, but not abnormally fat.

3.—*George S.*: Died at age 67, having been paralysed for many years. No details available. Is known to have had a family, but these cannot be traced.

4.—*Charles S.*: All records suggest that he was not affected. There are now alive various grandchildren and great-grandchildren of his; not all of those living have been interviewed. His son, Aeneas, died unaffected in 1906, aged 59, and his family of five sons and five daughters (aged 45 to 60) are alive and unaffected. No case of the disease is known to them as occurring in any of the descendants of Charles S., and his issue has been omitted from the table.

5.—*Thomas S.*: first became aware of the onset of the malady at about the age of 45, and, realizing its nature, became addicted to alcohol and died at 50, in 1859.

6, 7, 8 and 9.—All lived to middle age, married and had descendants. No myopathy.

10.—A female, became affected in middle life, and died at the age of 65.

11.—A female, became affected late in middle life. No details available.

12.—A male, first evidence of weakness at about 45 years of age. He was a powerfully built man who, in his youth, had performed feats requiring an abnormal amount of strength. He died at 70; was myopathic and adipose.

13.—A female, died at 74, having suffered from the disease for many years. Was myopathic and adipose.

14.—A woman, unaffected.

15.—Born about 1825. Was of Herculean strength and endurance; nicknamed "Hit-away Harry," as a boxer in his youth. Later, nicknamed "Harry the Rapp," on account of his stamping gait. He became progressively weak in the legs from the age of about 40, but lived to nearly 70. Myopathic (including hypertrophic stage) and adipose.

16 to 40.—None of these cases (some examined personally) show any myopathy.

41.—No disease.

42.—Myopathic and adipose. Died twenty years ago; not examined personally.

43 to 45.—Normal; no examination.

46.—A male, aged 72 on first examination in 1923, is the oldest living member of the family. Here the symptoms began at the age of 50 with painful cramps in the calves and in the lumbar region. Later a progressive

loss of power in the legs developed and during the last two years the arms and hands have become involved. Prior to the onset of his symptoms he had shown the Herculean proportions and capacity so typical of the family. He was by profession a furniture remover, and at the age of 30 could carry a piano on his back without assistance, and would work at his trade for twenty hours at a stretch. If a piece of string were tied round the arm when at rest he could snap it with ease merely by contraction of his biceps. He walked with the "peacock strut" characteristic of the affected members of this family.

On examination (1923) the clinical picture is one of an unusually well-built man, largely bedridden on account of great muscular weakness. There is no obvious wasting in the legs, the calf muscles being of average size but giving the impression on palpation of being more fibrous than muscular. The left vastus internus is much shrunken, and there is moderate atrophy in that of the right side; the main weakness is however in the ilio-psoas muscles. The feet are unusually short. The approximate strength of the anterior tibials is 25 per cent. and of the calf muscles 20 per cent. All the tendon-jerks are entirely absent.

The arms and fore-arms show no atrophy or hypertrophy, but all the intrinsic muscles of the hand are moderately atrophied, especially the first dorsal and other interossei. The pectoralis major is normal; the right biceps and triceps about 40 per cent. of normal and the right deltoid 20 per cent., although these last muscles are of normal size. The left arm is similarly affected, but here the power is about 60 per cent. of the normal. Neither scapula is winged. There are no arm-jerks. No fibrillary tremor was observed in this or in any other case.

The extensors of the neck and the sternomastoids are normal but there is no jaw-jerk.

Re-examined 1931, aged 80.—General health has remained extraordinarily good. The weakness of his legs has gradually progressed until he is now only able to walk with the aid of crutches. He can only rise from a sitting position with the aid of his arms and hands. Gets tired and knees sag after standing for a few seconds.

The left hand began to waste at the age of 70, the right soon after. Wasting is now evenly bilateral in the hands. Seven years ago he sustained a right Pott's fracture.

Muscles affected.—In hands, chiefly the first and second dorsal interosseous muscles; abductor brevis hallucis, slightly affected; flexor brevis hallucis, barely appreciable action; the hypothenar eminences are normal. Flexor muscles of the fore-arm very weak, so that there is dorsiflexion of the hand during grip. Pectoral muscles excellent on both sides. All shoulder-girdle muscles good, but the spinati are not so big as would be expected in one of his muscular development. Abdominal muscles fair. Erectores spinæ, thin. Extension of knee 20 per cent., extension of ankle 10 per cent., flexion of knee 20 per cent., flexion of ankle 10 per cent. Gluteal group 25 per cent., ilio-psoas 10 per cent.

Measurements.—(Maximum circumference). Fore-arm right $9\frac{1}{2}$ in., left $9\frac{1}{2}$ in.; arm, right $11\frac{1}{2}$ in., left $10\frac{1}{2}$ in. Biceps very weak. Triceps moderately weak. There is general failure of power below elbow, but no absolute loss.

Reflexes.—No arm-jerks elicited, no ankle-jerks, no knee-jerks, no plantar reflexes.

Circulatory system.—Shows chronic, gross œdema of both legs from the mid-leg downwards, pitting of 2 cm. Blood pressure 184/100. Rather softly acting heart, otherwise normal. Slight œdema of the loins is present.

47.—A male, now aged 68. A thin man, who has recently developed atrophy of both hands (mainly involving radial interossei and thenar eminences, leaving hypothenar muscles normal). No weakness of legs. No ankle-jerks present. The knee-jerks can be obtained on reinforcement. *Forme fruste* of myopathy without adiposity. See photograph (fig. 7).

48.—A man, believed to be unaffected. Died unmarried at age of 50.

49.—A female, born in 1856, now alive; began to have symptoms between the ages of 30 and 40. She had never possessed an abnormal degree of strength and the onset was painless, the patient merely noticing a tendency to fall over any slight projection, with subsequent difficulty in rising. During the last four years weakness in the arms has become a feature.

The lower limbs show an exactly similar condition to that in Case 52, except that the loss of power is even more marked (to about 30 per cent. of normal).

In the hands there is considerable atrophy in the small muscles, elsewhere there is but little. Power in the arm and fore-arm groups generally is subnormal and all the tendon-jerks are absent.

Myopathy; moderate degree of adiposity.

50.—A woman, died at the age of 64. Walked badly in her later years. Myopathic.

51.—A woman, aged 56. Began to be affected at 49. Adipose and myopathic.

52.—A male, has reached 57 years of age (1922). When 34 years old this patient suffered from a severe attack of acute rheumatism, and on rising from his bed noticed a marked weakness of his lower limbs which contrasted sharply with his previous muscular strength, which again was very much above the average. Unlike most of the other cases the onset here was unaccompanied by cramps and was indeed quite painless. He has not been aware as yet of any loss of power, though there is an early atrophy of the intrinsic muscles of the hands.

Examination shows considerable atrophy of the calves, the other muscles of the lower extremities being diminished in size to a less degree. The foot is short and Z-shaped and there is slight contracture of the tendo-Achillis. Muscular power is everywhere less than normal. The gait is similar to that described in Case 89. Moderate degree of adipositas universalis.

In the hands an early atrophy of the radial interossei and of the thenar

eminence is seen, but none is obvious in arms or fore-arms. Muscular power here is a little below the normal and the tendon-jerks are absent in both legs and arms.

Re-examined 1931.—Aged 66. Can just walk alone without any assistance. In all circumstances the patient keeps erect in walking. To get upstairs he uses his hands. Evidently his greatest loss of power is in quadriceps and ilio-psoas group.

Size of legs.—Now general atrophy. Right thigh 16 in., left thigh 16½ in.; very thin calf, right 11 in., left 11½ in. Dorsiflexion of ankle, right 10 per cent., left 15 per cent.; flexion, plantar, right 10 per cent., left 15 per cent. Extension of knee, right 10 per cent., left 10 per cent. Hamstrings, right 30 per cent., left 30 per cent. Flexion of hip, left 5 per cent., right 5 per cent. Extension of hip, 15 per cent. Knee-jerks and ankle-jerks absent. No pseudo-hypertrophy. No power of flexion or extension of toes. Feet show tendency to Z-shaped contracture. All muscles are rather tough and hard. Normal range of movement at knees and hips, but only moderate at ankle. Slight contracture in normal position, so that flexion and extension are both limited.

Hands.—There is considerable loss of grip and a tendency to extension of hand on fore-arm during grip. There is considerable atrophy of interossei of both hands. Both arms of moderate power. Pectoral and shoulder-girdle muscles good.

Arm measurements.—Left 10 in., right 10 in. Fore-arm, left 9½ in., right 10 in. Hand, left 8½ in., right 8½. Atrophy chiefly of first dorsal interosseus and abductor pollicis. Each hand tends to adopt the *main en griffe* position. All muscles have less power than their size would indicate. He cannot rise from the floor alone. No pseudo-hypertrophy. Myopathic and adipose.

53 to 56.—None now alive. All died between ages of 25 and 50. Believed to be unaffected but record uncertain. No. 55 died soon after birth of 118, and at the age of about 30.

57 to 59.—Believed unaffected. None now alive, not examined.

60.—Began to be affected at age 30. Died in infirmary where he had lain for twenty-two years. Had tumour of face (? lipoma). Myopathic and adipose.

61.—Discharged from Army with paralysis of legs in 1867; died 1884. Myopathy.

62.—Died in 1914. Used to have a "waddling gait," and "had to put his hands on his knees to get out of a chair." Myopathy.

63.—Had a waddling gait and the "S. tap" (clicking of the heels in walking). Died in infirmary in 1922 after years of paralysis. Myopathic.

64.—Was attacked at 25, and needed two sticks to get about. Died of cancer at age of 45. Myopathy.

65.—Required support to get about in later years. Often fell down when crossing roads, &c. Died of dropsy in 1892. Myopathy and adiposity.

66.—Died in 1908, aged 73. Was very fat, reaching 20 stone weight (280 lb.). Had no muscular weakness. Died of septicæmia. Adipose, not myopathic.

67.—Adipose, died of dropsy about 1900. Began to be affected in legs at age 60, and by age 68 could not get up alone from her chair. Age at death, 70. Adipose and myopathic.

68.—Died after many years of progressive paralysis at age 70, in 1913. Could not stand alone for years before death. Adipose (250 pounds) and myopathic.

69 to 79.—All normal.

80 to 88.—A series of children, nine in all, none of whom lived to puberty. Cause of deaths unknown.

84 to 88.—All normal.

89.—A man, born in 1874. The first symptom in this case was at the age of 42; when walking there developed a sense of constriction in the left calf which increased in severity until it became actual pain and the movement had to be suspended. At this time the left calf was considerably larger than its fellow. The pain recurred whenever walking was attempted for more than a few minutes and the calf gradually increased in dimensions. His medical adviser was consulted and eventually a radiograph of the limb was taken, which, however, revealed no cause for the swelling. The patient then visited a surgeon who diagnosed a subaponeurotic lipoma and undertook an operation for its removal. Nothing but muscular tissue was found and unfortunately none of this was removed for microscopical examination. Following the operation there was a progressive diminution in the size of both calves which later spread to the muscles of the thigh, and accompanying this a gradual loss of power. The pain became a less noticeable feature and only a dull aching in the lumbar region, when walking is attempted, remains. The arms are not affected. Here again the patient had previously possessed unusual strength and powers of endurance. He could, in his youth, perform feats at once the source of admiration and of despair to his acquaintances. He could raise a 56 lb. weight between the thumb and first finger of each hand. He could climb a flight of stairs with a sack of corn weighing 500 lb. on his shoulders. On one occasion he attended a fair where a performing bear was wrestling with his keeper, and in response to a challenge succeeded in throwing it.

Examination (1923) shows a well-nourished man of 49 years of age with a marked tendency to adiposity. The lower extremities are somewhat slender when compared with the rest of the body, and the feet are short. The maximum circumference of the leg below the knee is 15 in. as opposed to 17½ in. when he was at his maximum development. This bulk does not represent muscular tissue, of which but little can be detected, but is mainly due to fatty and fibrous tissue. There is considerable loss of power, especially in the peripheral part of the limb, but the small muscles of the foot are unaffected. The approximate strength of the various muscle groups is as follows: Extensors of thigh, 30 per cent.; flexors of thigh, 30 per cent. Abductors of thigh, 60 per cent.; adductors of thigh, 30 per cent. Extensors of knee, 30 per cent.; flexors of knee, 30 per cent. Extensors of foot, 20 per cent.; flexors of foot, 20 per cent. Invertors of foot, 20 per cent.; evertors of foot, 20 per cent.

The knee-jerks and ankle-jerks are absent and the plantar reflexes flexor. There is no lordosis.

The patient stands with the legs far apart in order to maintain the upright posture. If the legs are approximated he sways backwards and forwards a few times and then falls. In standing, the knees are held rigid in a position of slight hyperextension, and the gait is waddling in order to enable the moving leg to be thrown forwards to clear the ground. The heel is first brought into contact with the floor with a sharp click, and the toes of the static leg are firmly flexed as the man moves forwards. As the result of this there is a callosity over the interphalangeal joint of each great toe. If the semi-conscious effort to keep the knee extended is relaxed, the leg doubles up, and the patient falls. Once down he cannot raise himself without the assistance of a chair or some similar object. He places his hands on the chair, draws up first one knee and then the other, and then with his feet widely separated raises his body with the aid of his arms, extends his knees, and once more regains the upright position.

He cannot walk upstairs without the assistance of his upper limbs.

The arms are throughout of large size and power, and the tendon-jerks here are present.

Re-examined 1931.—Aged 57. Walking has gradually deteriorated during the last ten years, and if he falls on his knees he cannot get up without help. At first he was able to get up with the aid of a post, but two years ago he had a bad fall on to his knees and sustained a right inguinal hernia. Recently he has been getting cramp in the thighs after sitting for a few hours. During the past three years there has been a considerable degree of wasting in both arms.

Nervous system.—Marked weakness was present in all the following muscles: Left anterior crural muscles to a greater extent than in the right, which were also weaker than normal. Hand grips definitely weak, wrist movements good, dorsiflexors of the feet very weak. Muscles of both hands equally involved. Atrophy affects chiefly the abductor indicis, abductor pollicis, thenar eminences and the opponens pollicis of each hand. Calf, left 14 in.; calf, right 14½ in. Sensory functions: tactile, pain, temperature and joint sensation are normal. Vibration sense absent in the legs. Co-ordination good. All tendon-jerks absent; abdominal, reflexes absent and plantars flexor. There is no weakness of any of the muscles supplied by the cranial nerves. Cholecystectomy was performed (two weeks previous to present examination) for acute cholecystitis.

This patient has three children, of whom the eldest and the youngest show an early stage of the disease (Cases 156 and 157). See photographs, figs. 4, 5 and 6.

90.—Aged 55, examined and found normal.

91.—A woman born in 1877; has noticed this year (1922) that she has some weakness in the legs. She cannot stand on the toes nor rise naturally from a chair, and she has developed the typical family gait. The calves are, proportionately to the rest of the body, enlarged. The left measures 15½ in. in

maximum circumference and the right $16\frac{3}{4}$ in., the former being the weaker. The ankle-jerks and knee-jerks are absent. She is markedly adipose, weighs 186 lb., height 5 ft. 1 in.

On re-examination in 1931: aged 54, weight 210 lb., height 5 ft. 1 in. Can still walk with the aid of a stick. In the arms the muscles are all very big, especially in the fore-arm, but are beginning to get weak. There is much panniculus adiposus. The only atrophy is in the 1st dorsal interosseus. Tendency to hyperextension of knees in walking; tends to fall backwards when standing and has to keep moving in order to keep erect. The weakest movements are flexion and extension of the hips, which are only about half normal power. Flexion and extension at knees nearly normal. Rising from chair is only possible either with assistance of her hand or a full swing of body forwards.

She has three children, the two eldest being in different stages of myopathy.

92.—Normal; not adipose. Aged 51.

93.—Died at 31. Neither myopathic nor adipose. Suffered from epilepsy.

94 to 101.—All these men, whose ages range from 27 to 44, are normal in appearance, and are not adipose. None show myopathic weakness. Tendon-jerks in all are normal.

102 and 103.—Normal according to report. Their present ages are 44 and 37; neither has been examined.

104 to 107.—These four (eldest 33) are all said to be normal. None examined.

108.—A man, aged 31. Began to show weakness of hip muscle two years ago. Typical family gait. No leg reflexes. Moderately adipose; myopathy.

109 to 112.—These four, eldest 33, are said to be normal. Not examined.

113.—Woman, aged 41, examined, normal.

114.—Aged 39, normal.

115.—A man, aged 35 at first examination in 1921, left-handed, had pain in the thigh and calf muscles towards the end of his day's work. He has noticed no weakness but is a strong man who can lift four to five hundredweight with ease.

The legs show a remarkably good musculature with no sign of any disease except that the knee-jerks are absent. The arms again are of more than average development and here the jerks are present. He has five children, of whom the eldest alone (163) shows any abnormality.

Re-examined 1931.—Aged 45, is still in the hypertrophic stage. Calves, right $15\frac{1}{2}$ in.; thighs, right $19\frac{1}{2}$ in., left 19 in. All movements of ankle free and powerful. Power in all muscles of flexion and extension of ankles and knees about 120 per cent. Psoas iliacus, 90 per cent. Gluteal group, 95 per cent. Hands, full size and power. Knee-jerks, nil. Ankle-jerks, present both sides. Biceps-jerk, also just present. Triceps-jerk, absent. Arm measurements, right arm $12\frac{1}{4}$ in.; right fore-arm, $11\frac{1}{2}$ in.; left arm, 12 in.; left fore-arm, $11\frac{1}{2}$ in. There is a strong suggestion of true hypertrophy of both calves. No atrophy of pectorals. Musculature is far ahead of normal in

general size and power. The only failure of power is slight, in flexion of hip. In the legs there is definite hypertrophy. He is so far unconscious of any weakness. Myopathic and of moderate adiposity (see figs. 1, 2, 3, and 4).

116.—A woman of about 45 years of age. All reflexes normal. Moderate adiposity. No myopathy.

117.—A male, aged 34, has been affected for four years. He suffers occasionally from attacks of giddiness causing him to fall; in these there is a feeling of extreme heaviness in the lower limbs, during which they cannot be controlled by an effort of the will. On exertion he has severe cramps in the muscles of the calves and thighs.

Examination shows an apparently well-developed man, though not so Herculean in his proportion as some of his relatives. There is pseudo-hypertrophy in both thighs, but both knee-jerks can be obtained on reinforcement. The ankle-jerks are absent. No atrophy is present anywhere, although he says the muscular power is very definitely less than it was five years ago. The right vastus externus shows well-marked myotonic contraction on light contraction, and to some extent the vastus internus and rectus femoris share in this phenomenon. On strong contraction the rectus femoris goes into spasm similar to that seen in Thomsen's disease.

There is no lordosis. The gait is typical, and the patient rises from the prone position in the manner usually adopted by subjects of pseudo-hypertrophic palsy, though with much difficulty. The arms have a normal degree of power, but the tendon-jerks are absent. The sternomastoids are normal.

Re-examined 1931.—Aged 44. Weight 168 lb.; height 5 ft. 4 in. Gait substantially normal. Can rise from chair nearly normally. Muscles of legs above average size. Calves tougher than usual. No contracture at ankle.

Power.—Dorsiflexion of ankle, right 75 per cent., left 75 per cent. Plantiflexors, right 100 per cent., left 100 per cent. Knees, extension 100 per cent., flexion 100 per cent. Right hip, extension 40 per cent., flexion 40 per cent. Left hip, extension 50 per cent., flexion 40 per cent. Ankle-jerks and knee-jerks are absent.

In the arms and shoulder-girdle, all muscles are about normal in size and consistency. Power in arms normal throughout. No atrophy of hands. Muscles of neck all normal. All tendon-reflexes absent in arms and legs.

Measurements.—Right arm 12½ in., left arm 12 in. Right fore-arm 11½ in., left fore-arm 11¼ in. Right calf 13 in., left calf 13½ in. Still has tendency to myotonic contraction of thigh muscles but no fibrillation was present. Adipose and myopathy. Tendency to myotonic contraction.

118.—A man aged 40 who was first seen in consultation in 1923. Always big and strong in his early manhood. Took a commission in the Great War (1915); could march twenty miles a day with ease at commencement, but when he left the Army in 1919 used to get pains in calf muscles and to tire after a few miles: gradually less capable of long standing and walking. In 1923, all muscles much above normal size, but in legs of barely normal power. Extension of knees and flexion of hips definitely weak (about 60 per cent. each)

No reflexes at ankle, knee or in arms. No wasting anywhere. Adipose (weight 194 lb.), height 68 in. Found to have hyperpiesia and chronic nephritis. Muscular power in legs gradually declined and atrophy of the muscles of the hands began in 1927. Died at age of 48, of heart failure, in January, 1931. Fragments of muscle were obtained (see further description, and photo-micrographs of muscle sections in Plates I and II.)

119.—Died young. No history available, but believed by brother to have been normal.

120, 121.—Two sons aged 60. The second normal on examination; the first reported to show no sign of myopathy, but is fat; has been a boxer, age now 42.

122.—Man, aged 56; examined, normal.

123.—Died at age 5, in 1887. Could never walk. Could "only riddle himself along the floor," i.e., was presumably a "buttock walker." No other facts available.

124 to 126.—Three women, aged 47 to 60, all examined and found normal.

127.—Died young, unaffected.

128.—A woman aged 43; examined, found normal.

129.—Died in childhood.

130.—Born in 1886. Began to walk badly at age 15, married her cousin (not of the S. family), emigrated to America. Has been bedridden for ten years. Has a daughter who is said not to be affected. Myopathic and probably adipose.

131.—A man of 73 (born 1858). Began to notice weakness of legs at age 57, gradually worse since. Legs now severely affected, but can still just walk with the aid of two sticks. No affection of hands. No tendon-jerks. Myopathic and adipose.

132.—A woman, who died at age 35, unaffected. Not examined.

133 and 134.—Died at ages 50 and 40, neither known to be affected. Not examined.

135.—A thin man, aged about 50, no evidence of disease. Reflexes normal.

136.—A thin woman, aged 47. Began to have difficulty in walking at 11 years of age. Never hypertrophic, no pseudo-hypertrophy. Gradually increasing weakness in legs; no pain at any stage. First seen in General Hospital, Birmingham, 1916. Weight then 98 lb., height about 5 ft. 1in. Had then atrophy and weakness of severe degree in all muscles of hips, thighs and legs. All jerks absent. Diagnosed as case of peroneal atrophy (Charcot-Marie-Tooth). Seen again 1923, and re-examined 1932. Atrophy more advanced in lower extremities, but no single muscle entirely paralysed; average power 10 per cent. to 30 per cent., flexion of hips being weakest. Now getting atrophy of radial group of intrinsic muscles of hands (not in hypothernar group). Can still get about with crutches. Myopathy; no adiposity.

137.—Died at age 9; no myopathy.

138.—Died at age 19; no myopathy.

139.—Died young.

140.—Three other children, died in infancy. No myopathy.

141 to 150.—None affected. Several were examined in 1921, none re-examined. No record of adiposity.

151 to 155.—None myopathic or adipose. All now in middle life.

156.—Male, aged 25. Of moderate muscular development, not particularly adipose. No symptom of weakness. Knee-jerks and ankle-jerks are all absent, even on reinforcement. Incipient myopathy.

157.—Female, aged 19. Of unusually fine muscular development (true hypertrophic type). No weakness, but all tendon reflexes absent in lower extremities. See further description in text ("Hypertrophic stage").

158.—A female, aged 21. Since an attack of tonsillitis at the age of 12, the patient has suffered from a sudden giving way of the knees, especially when she is fatigued, which prevents her from running, and in consequence of which she was made goalkeeper in her hockey team. There is no pain in the muscles. The frequency of these falls has increased during the last two years, and they may occur three times in one day. She has difficulty in ascending stairs and is liable to trip over any slight elevation, such as a doormat. About the age of 14, and again recently, she suffered from "fainting attacks" associated with a "far-away" feeling and lasting a few seconds at a time. These sometimes recur five times in one day and then not again for a number of days. Last year, following an attack of gastritis, the muscular symptoms became more severe.

In height the patient is 5 ft. 9 in., with weight constant at 131 lb. There is no wasting of muscles but the foot tends to be Z-shaped, and there is a slight contracture at the ankle, in spite of which the foot can be voluntarily dorsiflexed beyond a right angle. There is no lordosis.

The measurements of the limbs are as follows:—

Calf (maximum), right 14 in., left 14 in. Thigh margin (6 in. above upper border of patella), right 17½ in., left 17½ in. Fore-arm (maximum), right 9½ in., left 9½ in. Arm (maximum), right 9½ in., left 9½ in.

Muscular power is approximately as follows:—

Plantar flexion and dorsiflexion of foot, right 60 per cent., left 60 per cent. Quadriceps, right 20 per cent., left 20 per cent. Ilio-psoas, right 50 per cent., left 50 per cent. Hamstrings, glutei and arm muscles, normal. The knee-jerks are both absent, as is the left ankle-jerk. The right ankle-jerk appears feebly on reinforcement. The arm-jerks are normal.

In this case it was possible to ascertain the electrical reactions of the muscles. There exists a general diminution of the response to faradism, while to the galvanic current there is a normal sharp contraction.

In walking there is the same hyperextension at the knee seen in the other cases, and the girl walks upstairs with knees rigid and with assistance from the hands and arms.

Re-examined 1931.—Aged 29. Height, 5 ft. 8½ in. Weight 176 lb.

Chief weakness is in the ilio-psoas group, which is reduced to 15 per cent. Extensors of the knee are gradually getting worse, and she cannot walk

upstairs or cross knees without the aid of hands. Glutei normal; adduction and abduction at the hips diminished but not greatly so. Erector spinæ strong. No lordosis. Muscles of the shoulder-girdles and the first dorsal interossei are normal. Ankle-jerks and knee-jerks absent. Myopathy; adipose.

159.—A male, aged 15, shows no abnormality save that the ankle-jerks are present only on reinforcement.

Re-examined 1931.—Aged 23. Has played Rugby football regularly. There is a tendency to hyperextension at the knees with some projection of the calf backwards.

Calf measurements.—Right $15\frac{1}{2}$ in., left $15\frac{3}{4}$ in. Knee-jerks and ankle-jerks present on reinforcement. Probably no myopathy.

160.—A boy, aged 13 (in 1921). Small build, normal in all respects. Re-examined in 1931, still fully normal; no adiposity.

161.—A boy, aged 12. Has mitral regurgitation. Of under average build. No sign of myopathy.

162.—A normal boy, aged 18, average build; reflexes normal.

163.—A girl, aged 13, no weakness; has complete absence of knee and ankle jerks. No adiposity.

164 to 166.—Three normal children (ages 10 to 14). Reflexes present in arms and legs.

167.—A baby, aged 4, rather fat, all jerks normal.

168.—A baby, aged 2. Deaf and dumb. Normal reflexes.

169.—A man, aged 22. No weakness. All reflexes normal. Very thin.

170.—A boy, aged 16. Average build, rather thin, normal throughout.

171.—A man aged 20. Has mitral stenosis. No loss of reflexes or muscular weakness.

172.—Girl, aged 19. Average build, normal reflexes.

173.—Girl, aged 15. Muscles above average size; has no biceps, triceps or supinator reflexes, but knee and ankle reflexes normal. Probably myopathic.

174.—A boy, aged 11. All muscles of lower limbs above average size. Knee-jerks just present, arm-jerks absent. Not adipose. Probably myopathic.

175.—A girl, aged 4. No abnormality detected.

176.—A baby, aged 12 months. All reflexes normal.

177.—A girl, aged 18. Has infantile hemiplegia of light degree, with Jacksonian epilepsy. Reflexes present. Thin, no myopathy.

178.—Not seen, reported normal.

179.—A normal man. No adiposity, no myopathy.

181 to 186.—All examined, normal.

187 to 196.—All normal except 188: a youth who is deaf and dumb (congenital); see text.

197 and 198.—Ages 52 and 30. Examined, normal.

199.—A man, aged 52. Early atrophic stage. Began to show weakness at about age 45. Now has to use his hands to rise from a chair. Hands normal. Reflexes absent. Adipose and myopathic.

200.—A man, aged 37. Adipose, weight 224 lb. Examined, no evidence of myopathy. His father "thinks he will become so because he is fat."

201 and 202.—Examined, normal.

203.—A woman, aged 48. Difficulty in walking for last twelve months only. Adipose, myopathic.

204 to 208.—All adults (ages 27 to 38); all examined, normal.

209.—A young woman, aged 22. Thin; has no knee-jerks or ankle-jerks, but no evidence of weakness. Probably myopathic, no adiposity.

210 to 242.—Most of these, all adults, have been examined and found normal. No report of weakness in the others.

243 to 281.—Most of them have been examined. Ages range from babyhood to 25. All presumed normal; no case found with absent reflexes or weakness.

282 to 284.—Three babies. No examination.

REFERENCES.

- [1] ADIE, W. G., and GREENFIELD, J. G. *Brain*, 1923, **46**, 78.
- [2] BATTEN, F. E. *Quart. Journ. of Med.*, 1910, **3**, 313.
- [3] *Idem.* *Proc. Roy. Soc. Med.* (Sect. Neurol.), 1910, **3**, 92.
- [4] BRAMWELL, E. *Ibid.*, 1922, **16**, 1.
- [5] CAMPBELL, C. McF. *Rev. of Neurol. and Psych.*, 1906, **4**, 192.
- [6] COTTIN, E., et NAVILLE, M. F. *L'Encephale*, 1912, **7**, 401.
- [7] CREW, F. A. E. "Organic Inheritance in Man," London, 1927.
- [8] DAVIDENKOW, S., u. KRYSHOWA, N. *Zeit. f. d. ges. Neur. u. Psych.*, 1930, **125**, 81.
- [9] DIEHL, F., HANSEN, K., u. UBISCH, G. v. *Deutsche Zeit. f. Nervenheilk.*, 1927, **99**, 54
- [10] EBB, W. *Ibid.*, 1891, **1**, 18.
- [11] EULENBERG, A. W., u. COHN, T. *Neur. Centralbl.*, 1911, **30**, 963.
- [12] FLISCHER. *Arch. f. Ophthalm.*, 1918, **96**, 91.
- [13] GOWERS, W. "Pseudo-Hypertrophic Muscular Paralysis," London, 1879.
- [14] HOFFMAN, J. *Deutsche Zeit. f. Nervenheilk.*, 1898, **12**.
- [15] KREFFERSTEIN. Quoted by Weitz.
- [16] KRABBE, K. H. *Journ. of Neurol.*, 1930, **10**, 289.
- [17] LANDOUZY, L., et DÉTERINE, J. *Rev. de Méd.*, 1885, **5**, 81.
- [18] L. DE LISI. *Riv. di Pat. Nerv. e. Ment.*, 1926, **31**, 390.
- [19] MARINA, A. *Deutsche Med. Woch.*, 1908, **34**, 1087.
- [20] MINKOWSKI, M., u. SIDLER, A. *Schwets. Med. Woch.*, 1928, **9**, 1005.
- [21] MORGAN, T. H. "The Theory of the Gene," New Haven, 1926.
- [22] NAVILLE, F., CHRISTIN, E., et FROMMEL, E. *L'Encephale*, 1923, **18**, 182.
- [23] NIWA, C. *Proc. Imp. Acad. Japan*, 1929, **5**, 287.
- [24] OPPENHEIM, H. Textbook of Nerv. Dis., English Trans., 1911.
- [25] ROBINSON, A. A. *Med. Journ. and Rec.*, 1925, **121**, 76.
- [26] ROBERT, J. *Brain*, 1922, **45**, 1.
- [27] SCHULTZ. *Deutsche Zeits. f. Nervenheilk.*, 1899, **14**.
- [28] SCHUMACHER. Quoted by Weitz.
- [29] SPILLER, W. G. *Journ. of Nerv. and Ment. Dis.*, 1907, **34**, 14.
- [30] *Idem.* *Brain*, 1913, **36**, 35.
- [31] *Idem.* *Lab. of Neuropath. Univ. of Penns.*, 1907, **3**, 1.
- [32] TIMME, W. Quoted by Robinson.
- [33] WEITZ, W. *Deutsche Zeit. f. Nervenheilk.*, 1921, **72**, 148.

FAMILIAL PERIODIC PARALYSIS. A DESCRIPTION OF SIX CASES OCCURRING IN THREE GENERATIONS OF ONE FAMILY.

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I.—INTRODUCTION

II.—DESCRIPTION OF CASES.

III.—GENERAL DESCRIPTION OF THE DISEASE—

- (1) *Ætiology.*
- (2) *Pathology.*
- (3) *Symptomatology and Course.*
- (4) *Diagnosis.*

IV.—DISCUSSION

V.—SUMMARY.

I.—INTRODUCTION.

THE recognized features of the disease we are about to consider are the occurrence of periodic attacks of flaccid paralysis of comparatively sudden onset, without obvious cause, with diminution or loss of electrical excitability in the muscles of the affected limbs and absence of the deep reflexes. The degree of paralysis varies in different attacks from a partial affection of one limb to complete paralysis of all the muscles of the trunk and limbs, with the occasional involvement of certain muscles innervated by the cranial nerves. Variation is also shown in the duration of the attacks as these may last from a few hours to three or four days, while in exceptional instances death has occurred at the height of an attack.

A case of periodic paralysis reported by Cavaré in 1863 appears to be the first record of this condition in the literature. In 1885, Westphal and Oppenheim gave a detailed description of an isolated case, and later in the same year Goldflam described the familial nature of the disease. Since then descriptions of cases have appeared at intervals, the most notable being a series described by Holtzapfel, in America, in which seventeen cases occurred in four generations of one family. In this

country Singer and Goodbody in 1901 were the first to describe a case of familial periodic paralysis, while later in the same year Buzzard described three cases, and Mitchell, in 1902, gave a description of a similar number. Since then, however, although occasional isolated cases have been recorded, I have been unable to find the records of cases occurring in more than one generation. Since the end of last century no advance has taken place in our knowledge of the disease, which still remains of extreme rarity, as altogether only about two hundred odd cases have been reported in the literature.

As in migraine, which has some points in common with familial periodic paralysis, one encounters insuperable difficulties in investigating the attacks, as these do not occur during the period of physical and mental rest with regular simple meals associated with residence in hospital. Particularly is investigation impeded from a biochemical point of view, for which it would be necessary for the patient to be on a diet of fixed composition in order to determine any variations preceding and during the paralytic attack.

In the family which I have investigated, there has been difficulty in inducing those affected to come into hospital when paralysis supervenes, as their familiarity with the course of the disease has caused them to refuse hospital treatment unless an attack was aggravated by some co-existing condition. Even in the case of two members in whom a fatal issue occurred at the height of an attack, the family doctor was not even called in before death took place, as the course, prior to the incidents which precipitated sudden death, did not alarm the relatives.

II.—DESCRIPTION OF CASES.

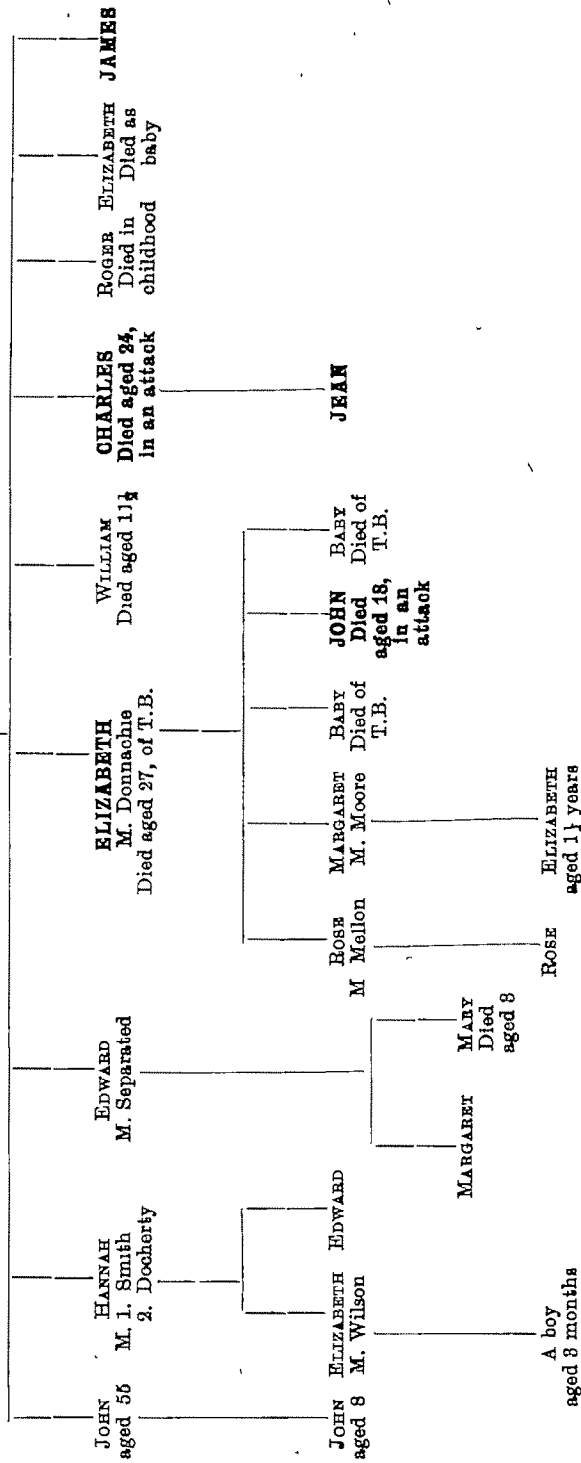
The paralytic attacks of three members of this family have not personally been observed by me, but the features of their attacks as reported to me are so similar to those experienced by the other members of the family that I have only remarked points in which they show any interesting differences.

In all those affected the paralysis was of a flaccid nature with the absence of the deep reflexes, and in no member of the family has there been any evidence clinically or serologically of a syphilitic inheritance.

(1) Edward W.: The first member of the family known to suffer from the affection lived to the age of 72 and died apparently from no definite illness, but just "old age." His attacks of paralysis were typical of those observed in the remainder of his family, but for fifteen years before his death he was free from attacks. He was an iron planer by occupation and an otherwise healthy man,

No History of the Disease.

EDWARD W.



and had not suffered from migraine or digestive troubles. As will be seen from the family tree he had nine children. His attacks commenced during the night and were foreshadowed by stiffness in the limbs, while the duration of each seizure varied from a few hours to three days. On one occasion he was paralysed on wakening in the morning at 6 o'clock, but had recovered so far as to be able to go to his work at 9.30 the same morning. Of his nine children, three died in infancy and three suffered from the disease.

(2) Elizabeth W. was the second of the original Edward W.'s nine children. Her attacks were similar to those which affected the other members of the family and commenced at the age of 18; she never suffered from any very severe attacks, the majority in her case being of the partial or abortive type, and she was never confined to bed for more than one day. She was married at the age of 19 and had four children, the second youngest of whom also suffered from the disease.

She died from pulmonary tuberculosis at the age of 28.

She was never seen by me and my information regarding her was obtained from her brother, James W., who also suffers from the disease, and therefore appreciates the points on which information is required. He informed me that her attacks had been less frequent and severe for some time before her death, and that the latter was in no way associated with one of the periodic attacks of paralysis.

(3) Charles W.: The attacks made their appearance at the age of 18 and though generally typical of the disease were more severe than those of his father in that speech was usually much affected, so that he was at times difficult to understand, and difficulty in swallowing was also present during the period of paralysis. Further, his attacks were more frequent, occurring two to three times a week and occasionally lasting forty-eight hours or longer, while emotion and exhaustion were in his case common exciting causes. He died at the age of 24 in an attack. On this occasion on wakening during the night he had felt an attack coming on and had risen from bed and "walked it off." On the following day, however, it recurred at 3 p.m., complete paralysis resulting with marked affection of speech and difficulty in swallowing. On the following day when his condition showed no improvement he was given a large dose of castor oil. This would not "go down" and some passed into the larynx, causing him to cough and choke and, so great was the weakness of respiration, that death ensued. This member of the family suffered from bulimia on the day preceding an attack and occasionally vomited clear mucoid fluid during his period of paralysis. His marriage was an unhappy one and his domestic life was one of disharmony; moreover he was wont to get his feet wet and this, and the cold at his work, were considered by him to be an exciting cause of the attacks.

(4) James W., is a butler. He was never robust, but on the other hand has had no definite illnesses. From the age of 6 years he suffered from periodic bilious headaches. When these occurred they were present on wakening in the morning and persisted all day until he went to bed at night. Vomiting occurred with some of the attacks of headache and this gave a certain amount of relief. These headaches occurred as a rule once a week and on many occasions were

so severe that he was unable to go to school. During these attacks he felt "poisoned" and unfit for anything until vomiting occurred or he went to sleep. There was no noted associated disturbance of bowel function. These periodic headaches persisted up till the onset of the attacks of paralysis, but disappeared within a year of the first of these attacks and have not since recurred. The first attack of paralysis occurred at the age of 18, and the next after a fortnight's interval; thereafter there was one attack a month till he was aged 23, when their frequency increased to once weekly.

He believes that cold and dampness of the feet predispose to attacks, but excitement and worry coupled with exhaustion appear to be factors of more importance. As is the case with many sufferers from migraine, he often feels exceptionally well on the day preceding an attack, and a voracious appetite coincides with this feeling of well-being; this was so marked that the other servants used to warn him when they noticed his exceptional appetite that he would be off duty the following day. If after a strenuous and worrying day culminating perhaps in a dinner party he had a meal late at night, which on such occasions usually consisted of rich food, an attack was almost certain. His longest attack, which lasted for four days, followed such a sequence of events, and during that period on being carried to stool two evacuations of the bowels took place.

He prefers sweet articles of food to meat, and is of the opinion that a meal which consists largely of protein, especially if consumed late at night, is likely to be followed by an attack.

In this case warning of an attack consists of stiffness of the limbs with a desire to stretch and move them, and such prodromata may precede the attack by two to three hours. However, unlike other sufferers from this paralysis, he has been unable to walk off an impending attack, but he has had on occasions short attacks followed after a few hours by a relapse; thus he was awakened at 3 a.m. with an increasing or complete paralysis, from which he had recovered by 3 p.m. the same day, and he has been able to do his ordinary work thereafter till bed-time, but during the following night the paralysis would recur and last for a similar period the next day; such relapses, however, have never occurred on more than two successive days.

Although in the majority of the attacks the paralysis has involved all the limbs, in a few instances the legs only have been affected, and still less frequently the arms alone have been involved.

The transition from severe paralytic attacks to minor abortive forms has been present for the last five years and coincides with a period of unemployment and accordingly with freedom from the long hours, rich food and strain of his occupation which previously appeared to be factors predisposing to attacks.

This patient is a small spare man of 5 ft. 4 in. in height and weighs 7 st. 6 lb.; his expression is habitually anxious and worried and he states that he has always had a sallow complexion. He is, however, well proportioned and there are no stigmata of degeneration and physical

examination revealed no evidence of any other organic disease. A fractional test meal demonstrated no free hydrochloric acid in any specimen up to two and a half hours after the gruel, and further evidence of inefficient digestion was obtained from the fact that digestion of starch had failed to take place throughout the same period, although the motility of the stomach appeared to be within normal limits. The Wassermann reaction was negative in both the blood and spinal-fluid and the latter showed otherwise no abnormality.

In the complete paralytic attacks the electrical responses to the faradic current were lost and were much weakened to galvanic stimulation, but in the minor abortive seizures which have succeeded the severe attacks during the last five years no abnormality of the electrical reactions has been noted. The basal metabolic rate was estimated on one occasion in the interval between attacks and the reading obtained was -3.5 .

The minor attacks of recent years have been characterized by stiffness and numbness affecting one or two limbs, sometimes with a temporary paresis of a few hours duration, and with these there has been no gastro-intestinal or other general disturbance which has attracted his attention. In the major attacks his skin has been usually pale and cold during the period of the seizure, but, as recovery commences, this has been succeeded by flushing and warmth of the skin with often obvious sweating.

(5) Jean W. This girl, now aged 23, is a daughter of Charles W., in the second generation of the family, who died during an attack of the disease. She was a normal full-time baby and was breast-fed for a year. At the age of 8 months she had "catarrh of the stomach" which was successfully treated, and she thereafter had no digestive complaints, but she has always suffered from constipation. After the age of 17 years she began to be troubled with periodic headaches which were always present on wakening in the morning, and thereafter increased in intensity during the day. These headaches were associated with a feeling of lassitude, vertigo and nausea, but vomiting did not occur as a rule and there were no visual phenomena. When the headache is near its acme she becomes very white and then there is frequently also a "cold sweat." At this stage there is usually a desire for fresh air, her respirations are deep and of a sighing nature, and she wants the windows in the room opened wide.

The first paralytic attack occurred in her nineteenth year when she was coming home from school. Her clothes had been soaked while going to school and while at work there she had felt stiff, but on leaving school she had to be helped on to the car as her legs were weak and uncertain. On reaching home three-quarters of an hour later she was quite unable to walk out of the car and had to be carried home.

The arms were slightly stiff, but there was no loss of power in them, neither was there any bulbar or sphincter symptoms. This attack passed away completely in about three hours.

The second attack occurred about three months later. It commenced

during the night about 4 a.m., when she awoke and called for assistance as she had a feeling of malaise and all her limbs were stiff. After having her limbs moved and rubbed she was able to go to sleep again, but woke at 7 a.m. unable to move any limb, but without difficulty in swallowing or breathing. The paralysis persisted for three days with no variation in degree and then gradually passed off. During its presence, although she was able to micturate on being supported on a stool once a day, presumably when the bladder became distended, no movement of the bowels took place until some hours after the attack had passed off. The next attack occurred after an interval of five months, when one morning on rising she was conscious of nausea and vertigo, which persisted after breakfast, while she was doing her usual domestic work, and even increased in degree. About 11 a.m. she went into the scullery to do something and while there was seized with vertigo and fell; she is said to have been unconscious for ten minutes and thereafter was found to be unable to move any limb, so was sent into hospital.

The sphincters functioned normally and there was neither dysphagia nor dysarthria. The paralysis persisted until she went to sleep, but she had completely recovered by the morning, although a sensation of stiffness persisted. Her condition was diagnosed by the house physician as hysteria.

Two months later another attack occurred. She had been out shopping in the afternoon after having done her usual domestic work in the morning, and as it was necessary for her to walk some distance she came home feeling rather tired. She was resting by the window when she felt her left hand stiff and this stiffness fairly rapidly affected in turn the rest of the arm, then subsequently the legs and then the right arm, along with weakness in the legs and also weakness of the left arm, necessitating assistance in getting her to bed. The legs became so much involved that she could not move herself in bed, and this weakness persisted until she went to sleep, but had passed away as before when she woke in the morning.

The next attack occurred three months later. On the preceding morning she had wakened with a headache, and had felt "out of sorts" and sick all day: she had cheese and toast with tea for breakfast, and for dinner at 2.30 p.m. she had Irish stew, potatoes, and a cup of tea. Her headache thereafter gradually disappeared, but she had no food at all during the remainder of the day and was out from 7 to 9.30 in the evening doing a message, and as the month was December she returned home feeling very cold. While sitting in a chair after her return she felt her right hand becoming numb and saw that it was slightly swollen. She was unable to move the fingers properly, and when she was going to bed at 10.30 p.m. she was unable to raise the left arm and required assistance in undressing. She slept well however, but on wakening at 7 a.m. she was unable to move any limb, sit up or raise her head from the pillow. She was able, however, to speak and swallow normally, and passed a large quantity of urine, but the bowels were confined. When seen by me at 11 a.m. the left hand was swollen, but no true oedema was present. She was unable to move any of her limbs and these, though not spastic, showed preser-

vation of muscle tone. She was still unable to raise herself in bed or move her head, but the respiratory muscles were functioning apparently normally, and there was neither dysphagia, dysarthria, or affection of any other cranial nerves. The tendon reflexes were not elicited, and the electrical reactions of the muscles while the paralysis was complete showed no response to either the galvanic or faradic current. She was pale, but there was no cardiac dilatation or arrhythmia, and the blood-pressure was 120 mm. Hg. systolic and 80 diastolic. Two hours later when recovery was commencing, she was still unable to move the left arm, but all movements were possible in the right, and she could move her head and sit up in bed. Voluntary movement was still impossible in the left leg save for a slight amount of flexion of the toes and foot, and on attempting to move this limb passively one was conscious of stiffness of the muscles controlling the hip- and knee-joints. In the right leg, although voluntary movement was possible in all groups of muscles, power was still much impaired. Three hours later she was able to walk and to use both arms though power in all the limbs was still below normal. The swelling of the left hand persisted for three hours more.

At the height of the attack there was no suggestion of any sensory impairment, and no paræsthesiæ apart from the usual feeling of stiffness, which lasted for the remainder of the day. The following morning she felt in her usual health, power was completely regained and there were no paræsthesiæ. During this attack she did not pass urine or defecate, but the bladder was not unduly distended even when complete power had been regained in the afternoon.

In her next attack she awoke at 5 o'clock one morning feeling her limbs stiff and weak, but went to sleep to waken again at 7 a.m. unable to move any limb or sit up, but able to move her head, speak and swallow normally. This attack though generalized was of short duration and she had gained considerable power by 11 a.m. and was able to walk and feed herself by 1 p.m. On the previous day, in addition to her usual work, she had scrubbed a floor and had felt very tired in the evening.

As a rule in the attacks which have a general distribution recovery commences in the legs before the arms and in the proximal muscles of the arms before those distal, but occasionally the intensity appears to have a hemiplegic distribution or one side of the body recovers before the other.

In addition to the general attacks which have been occurring at increasingly shorter intervals since the age of 18 this patient has had numerous minor or abortive attacks. These consist of transient attacks of stiffness, or of stiffness associated with some muscular weakness and may be only experienced in one limb, or in both legs or arms, or more rarely may show hemiplegic distribution. They may last from a few minutes to half an hour and are not associated with nausea, headache or digestive disturbance, and may occur several times in one week. She is convinced herself that cold and dampness predispose to attacks but does not connect them with exhaustion following excessive work or other cause, and the periodic headaches from which she suffered along with nausea

have tended gradually to disappear since she began to suffer from the paralytic attacks.

Her most recent attack was associated, and perhaps excited by, an attack of acute bronchitis and arthritis with pyrexia which for several days was about 102° F.

She had been ill for four days before coming into hospital, and for the last three of these she had been paralysed in all her limbs, and was unable to turn herself, sit up in bed, or even to raise her head from the pillow. She was thus on admission to hospital, and the deep reflexes were absent in the arms as well as in the legs.

A small measure of recovery took place within twenty-four hours, aided possibly by much application of heat, and although some slight movement of the arms was now possible she was unable for a further period of four days to use them for feeding or performing her toilet, while for the same period she remained unable to move in bed or even raise her head. Thereafter within twenty-four hours power was gradually but completely regained. In this attack complete recovery was much longer in taking place than in any other of my patients, and improvement was only noted when the acute bronchitis and fever were lessening. This suggests that the disturbance of metabolism associated with the pyrexia of her infection may have aggravated and maintained the intoxication, which I believe precedes and determines the paralytic seizures.

Breathing was much embarrassed during her first four days in hospital, and more so than appeared to be proportionate to the degree of bronchitis. Her cough was weak and ineffective, expectoration was carried out with difficulty, while the accessory muscles of respiration were in action during this period. Her voice also was more weak than normal, but there was no complaint of dysphagia; however, at the time of the pyrexia she was having no solid food with which difficulty in swallowing might have been made manifest. Her respiratory difficulty gave rise to some anxiety during this period, especially as her father had died in a paralytic attack from a spasm of coughing exhausting the weakened respiratory muscles.

During this attack urine was passed only at lengthy intervals, sixteen to twenty-four hours, when the distension of the bladder formed a sufficiently strong stimulus to promote evacuation, but the bowels moved normally following the administration of laxatives. Although no dilatation of the heart was noted, the pulse remained more frequent than was proportional to the pyrexia and respiratory rate, while the cardiac sounds, though pure, were of very poor quality.

During this attack an electro-cardiographic tracing taken at the time of complete paralysis showed no abnormality.

This patient had suffered from attacks of increasing frequency and severity since their onset five years ago. For the last year the knee-jerks have been absent, and for the last five or six months it has also been impossible to elicit the ankle-jerks, while the reflexes in the upper limbs are now all sluggish.

Moreover the muscles of the calves have now on palpation a firm, fibrous consistence similar to that found in some of the muscular dystrophies, but there is no obvious atrophy, and between attacks I have not been able to demonstrate any loss of power, although she herself says that her legs are easily tired.

A fractional test meal performed a year ago in the intervals between attacks showed a subnormal amount of free hydrochloric acid in all specimens, and even at the end of two and a half hours there was no evidence of starch digestion. I have never found any cardiac dilatation in any of the attacks which I have personally observed, but in one attack in her home, in which after being carried to stool she was subsequently placed in the chair by the fire, syncope occurred. Apart from her last and most severe attack in which acute bronchitis co-existed, there has been no evidence of involvement of the cranial nerves. The Wassermann reaction was negative in the blood and spinal fluid, and latter otherwise showed no abnormality. There was no stigmata of degeneration, but she is of small stature although well-proportioned like the majority of the members of her family.

Owing to the duration of her attacks it was possible with this patient to place her on a fixed diet and to estimate the distribution of the urinary nitrogen in collections over periods of twenty-four hours, both during a period of normal health and in a paralytic attack. The results obtained were as follows:—

	Total N	Ammonia N	Uric acid N	Creatinine N	
				Total (including creatinine)	Preformed
Normal period	6.66	0.259	0.100	—	0.217
Abnormal period ..	6.82	0.320	0.123	0.626	0.804

N = Nitrogen.

She has a stepfather and her home life is very unhappy, but it is difficult to assess the importance of anxiety and mental stress as exciting her frequent attacks, since we know that the frequency and severity are as a rule greatest at her age.

(6) John Donnachie was the third child of Elizabeth W., who herself suffered from the disease. He was a normal full-time baby, and apart from the usual infections of infancy and childhood appeared to have enjoyed normal health until the age of 17 years, when he had a mild attack of paralysis in the lower limbs associated with the common prodromal feeling of stiffness during the night; the attack itself only lasted some three hours and he was then able to go about. He was working in a shipyard and in three subsequent attacks, all of a mild character, he never lost more than half a day's work, partly possibly because his attacks also were as a rule towards the end of the week,

when they were sometimes associated with dietetic indiscretions. He was also subject to periodic bilious headaches of a migrainous nature, but these occurred independently and never merged into a paralytic attack. His fifth and final attack occurred in July while all his family except his father were on holiday.

One evening, having done his usual day's work, he had a supper of fish and chips, and admitted to having eaten to excess of this dish, but retired to bed feeling quite well. At 3 a.m. he awoke and called to his father to come and turn him in bed as he was unable to move any of his limbs, and had in all probability been wakened by the malaise noted in these attacks from the inability to change the position of the limbs and body in bed.

The paralysis persisted throughout the day and he was able to eat and speak without difficulty, but he passed no urine and the bowels were confined. On the following morning he was unable to lift his head from the pillow or to raise himself in bed, and in addition he had a feeling as if there was some obstruction in his throat which interfered with his breathing, and frequently said, "I wish I could get this out of my throat and I would then feel better." He was still able to swallow however, and there was no impairment of his speech. He was able to eat his dinner during the day, but with difficulty, and at 2 p.m. he vomited some undigested food. At 3 p.m. his father gave him some whisky and hot water "as his breathing seemed bad": this appeared to make him choke and more vomiting ensued, resulting in considerable exhaustion. He then appeared to improve slightly and asked for a cigarette from a friend who had come in to look after him while his father went back to work; this was given to him, but as it had to be held in his mouth and his breathing was shallow it is presumed that he inhaled a quantity of smoke, and since the respiratory muscles were too weak to compete with the paroxysm of coughing which ensued, his breathing failed and death occurred.

III.—GENERAL DESCRIPTION OF THE DISEASE.

(1) *Ætiology*.—Theories as to the causation of this disease have been numerous. Dana suggested that it might be symptomatic of a recurring poliomyelitis, that is, of a chronic infection with exacerbations; but from what we know of the protective influence of an attack of that disease, such a theory appears improbable quite apart from the wide clinical and epidemiological differences. Those who are unacquainted with the condition almost invariably suggest a hysterical basis for the seizures and it is probable that some mild cases are missed on this assumption. Holtzapple, though he attributed the seizures to spasm of the anterior spinal artery, described migraine as occurring in ten out of seventeen patients who had periodic attacks of paralysis. Five of his patients had attacks of paralysis associated with headache, and thirteen other members of the family, who never suffered from paralytic seizures,

had periodic migrainous attacks. In some of his cases the headache preceded the paralytic attacks, making its appearance in early childhood and then ceasing when the paralytic phenomena developed, but in other cases the headache continued throughout, alternating with attacks of paralysis. This, however, is the only series so far recorded in which migraine appeared to be a factor of ætiological importance.

Holtzapple also, from his theory of the ætiology, ascribes the permanent paralysis, occasionally found in those who had suffered from recurring attacks for many years, to a slow degeneration of the anterior horn cells from frequent disturbance of their nutrition. He advances as an additional causative factor defective nitrogenous elimination based on urea excretion. The frequency with which muscular exertion and cold have been described as exciting factors naturally suggested that products of normal or abnormal muscle metabolism were instrumental in bringing about the paralysis, and it is to be noted in this connection that forms of spastic periodic paralysis have been described by Rich and also by Collier. In the former's own family five members suffered from transient recurring spastic paralysis of the face as a result of fatigue and exposure to cold, while the latter describes two members of one family in whom spastic paralysis of a severe type could be produced at will by withholding food and giving exercise. In a family of travelling merchants described by Collier the attacks seemed to depend entirely on the absence of food, and this was demonstrated by the fact that if they dined at 8 p.m. no attacks occurred, whereas if they dined early or missed their evening meal an attack occurred with certainty.

Auto-intoxication in association with constipation, menstrual periods, or dyspepsia, is also mentioned, as are lack of exercise, emotional excitement and fatigue. Neustadter found an exceedingly high blood calcium (20 mg. per 100 c.c.) in his case, and from this finding it has been suggested that the high blood calcium might explain the failure of the muscle to respond to electrical stimulation from the occurrence of some disarrangement of ions.

Buzzard put forward two theories as to the ætiology: firstly, that a chemical or physical change in the muscle plasma alone was not only a possible but the probable explanation of the loss of muscular contractility; secondly, that the important part played by the muscular system in the control of lymph circulation points to an unstable condition of the latter, or an abnormal or toxic condition of the fluid itself as possible sources of the changes in the muscles.

Some writers have stressed an analogy with myasthenia gravis, as

in some cases of that disease attacks of paralysis lasting a few days and resembling those of family periodic paralysis have been described by Collins and others. But though the rapid exhaustion of the muscular power and the failure of the muscle to respond to electricity are suggestive, yet attacks of family periodic paralysis as a rule commence after the patient has been asleep for several hours, and even though muscular exertion on the preceding day has been blamed by many patients for exciting an attack, such exertion, even far short of causing muscular exhaustion, is by no means a constant factor. Moreover, the electrical reactions are not similar, and lymphorrhages are not a characteristic finding in family periodic paralysis, where also the main incidence of the paralysis is not in muscles enervated from the brain-stem.

In Mitchell's case an attempt to determine the toxicity of the blood-serum gave inconclusive results, but we know from the work of Mouzon and Turpin that injections of the serum of epileptic patients into the circulation of animals produced convulsions, which frequently had a fatal termination, whereas similar injection of serum from healthy people had no effect; further investigation of this nature is indicated in family periodic paralysis in view of the indefinite results so far obtained.

The transmission of the disease shows no characteristic features. In Holtzapple's series the disease was transmitted through a father who had attacks of paralysis in six instances; through the mother in four instances; through a father who had attacks of a migrainous nature in four instances, and through a mother who had migrainous attacks only in three instances. In nine instances the disease was transmitted through the father, and in eight through the mother. The members of this family who were thus affected were of varied occupations and intellectual attainments, and included a bricklayer, a seamstress, a school-teacher, a clergyman and a doctor.

The onset of the malady has been described as early as the second year and as late as the thirtieth, but it is most common for the first manifestations to appear about the years of puberty, and the severity is greatest between the years of 20 and 30, while it is during this period that the extremely rare instances of death occurring in an attack have been described.

More cases have been described in males than in females, but transmission may occur apparently equally through the members of either sex. Although the familial nature of the disease is now well established, isolated instances of the disease have been not infrequently reported.

(2) *Pathology*.—Autopsies have been exceedingly rare. In two of Holtzapple's cases in which post-mortem examinations were made, no pathological lesions were found to account for the disease. More recently Schmidt has reported two cases in which death took place at the height of an attack. In his first case the patient was said to have died of an intoxication from the alimentary tract, and hyperæmia was found in the nervous system as well as in other organs, but no specific lesions were discovered; unfortunately, the muscles do not appear to have been examined. The second patient, a brother of the first, died of cardiac failure in the course of a severe attack; here also there was hyperæmia of the organs and considerable cardiac dilatation, but nothing was observed in the central nervous system.

Biopsies of muscle have more frequently been performed. Oppenheim, Goodbody and Singer have described rarefaction and proliferative degeneration of the striated fibres with slight multiplication of their nuclei. They were not inclined, however, to attribute great importance to these findings, as they could not exclude the possibility of the changes being artefacts. Goldflam described a dissociation of primitive fibres with an increase in calibre and vacuolation, the sarcolemmal nuclei being also abnormally large. No interstitial inflammation, in fact no evidence of inflammation, and no nervous changes could be found. He compares these lesions with those found in progressive muscular atrophy. Schmidt noted similar lesions, and likewise compared them with progressive muscular atrophy and with the pathological findings in myotonia, but emphasized their resemblance to those found as the result of muscular ischæmia which he considered to be the basic cause of family periodic paralysis. He believed the paralysis in the latter condition is caused by a temporary arrest of the blood-supply to the muscles. All these results, however, are of little value, as the state of the muscles before, during and after an attack has not been studied, and it does not seem possible that gross alterations can occur at the moment of the attack. Further, we know that when the disease has been present for several years some permanent weakness in the muscles may develop, as noted in one of my patients.

Subsequent biopsies by other writers have given entirely negative results, so that the changes described above are now considered to be artefacts which have arisen in the course of preparation of the sections.

Holtzapple found a diminished excretion of urea in his cases, and noted also that the worse sufferers were those who showed the most marked diminution in the daily output of urea. His work was done,

however, at the beginning of this century, and there is no evidence that the patients were on a known intake of food or in nitrogen equilibrium before the amount of urea in the urine was estimated; so apart from there being no subsequent confirmation of the constancy of the decreased urea excretion in this disease, it is difficult to attribute much value to his findings.

Schlesinger, in an isolated case, found acetonuria in the majority of the attacks, and this was occasionally associated with albuminuria and the presence of hyaline casts, and Mitchell, Flexner and Edsall, from the examination on two occasions of the stomach contents of one of their cases, found that starch digestion was not proceeded with, and that there was total in acidity. Goldflam and Croft found the urine hyper-toxic to laboratory animals.

The relation of creatinine excretion to disease of muscular tissue has been investigated by many writers and most chemical-physiologists appear to believe that the excretion of creatinine in the urine bears a direct relationship to the amount of muscular activity, but in cases of family periodic paralysis the findings have been inconsistent. Taylor found that the creatinine output was diminished both before and during an attack. This was confirmed by Mitchell and Flexner, who also noted an associated diminution in the excretion of ammonia, and with the onset of recovery a return of the creatinine excretion to a normal figure.

Spriggs noted that creatinine is excreted in smaller quantities than normal when the bulk of the muscular tissue is diminished, as in the primary myopathies, and also when muscular activity and muscle tone are depressed by a pathological condition of the muscles or motor apparatus, as in myasthenia gravis and amyotonia congenita, but that the output is unaffected by loss of muscular tone through interference with the sensory path, as in locomotor ataxia. He considered, therefore, that creatinine was connected not only with the bulk of muscle but also with the normal development of muscular function, and while admitting that by far the greater part, if not all, of the endogenous creatinine in the urine is derived from muscular tissue, he held that creatinine is a product of the internal metabolism of muscle and not of its contraction.

The chemistry of creatin and creatinine has also been thoroughly investigated by Hunter, and the low output of creatinine in muscular dystrophies has been confirmed by many writers, notably by Burger and Meyer, and also by Gibson, Martin and Buell. Similar results

have been described in amyotonia congenita by Gettings and Pemberton, as also by Powis and Roper, and Pemberton has also found a low creatinine output in myasthenia gravis.

In family periodic paralysis we know that it is customary for the paralysis to make its appearance after a night's rest, but Cuthbertson, on investigating the influence of prolonged rest on muscle metabolism, found that in subjects who were in a condition of nitrogenous equilibrium, and who thereafter spent periods from five to thirty-two days in bed, there took place a rise in urinary nitrogen due to a proportionate increase in the amount of urea. The excretion of creatinine and uric acid, however, was practically unaltered.

In addition to the muscular dystrophies, the excretion of creatinine is largely reduced in extensive paralysis as well as in other conditions in which the activity of the muscles or their bulk is largely reduced, while during the process of wasting of muscles, as in the cachexias and after severe exercise, the amount increases.

In three cases of family periodic paralysis, Mitchell, Flexner and Edsall noted a marked diminution (3 to 80 mg.) in the creatinine output of the urine, along with a diminished excretion of ammonia preceding and during the paralytic attacks, with a sudden rise to normal (880 mg.) following recovery. From these findings it is thought that the attacks are due to a metabolic disturbance which is situated chiefly or entirely in the muscles themselves rather than that the attacks are due to retention of creatinine.

In my series it was only possible to have one patient on a fixed diet for a period between the attacks sufficiently long to get establishment of nitrogenous equilibrium and the urinary findings while in apparently normal health, and in this patient during subsequent attacks a definite increase in the excretion of creatinine in the urine was found.

(3) *Symptoms.*—The onset of the attacks has been described as occurring as early as the fifth year and as late as the thirtieth, but it is most common for the first manifestations to make their appearance about puberty. There is a tendency to a diminution in the frequency and intensity of the attacks after middle life, similar to what is common in migraine, and one of my patients was free from attacks for fifteen years before his death at the age of 70.

As in migraine, patients often say that on the day preceding an attack they have felt exceptionally well, and have not only accomplished an active day's work, but have taken exercise in addition. Similarly, bulimia is frequently present, and relatives have found it noteworthy

the amount of food required to satisfy the patient's appetite on these days. Moreover, not only is the appetite sharp, but there is often a craving for rich and heavy food, or even for specific articles of food, such as fruit or meat. The prodromata may be constant or variable in different patients, but they are usually the same for one individual, and sometimes for all those affected in one family. All the usual prodromata can occur without a typical paralytic attack ensuing, but most commonly they foretell an attack.

The majority of those affected waken in the early hours of the morning with a feeling of malaise, stiffness and weakness in the limbs, or they may even waken with the paralysis fully developed, when in such a case discomfort from inability to change the position of their limbs in bed appears to be the factor which arouses them from sleep. As a rule those patients who waken with the feeling of stiffness and weakness in the limbs are able to go to sleep again to waken at their usual hour with the limbs paralysed.

There is considerable variation in the *marche* of the paralysis. Thus a patient may waken completely paralysed, having had no warning of an attack, or having wakened at night with such prodromata as mentioned above; he may again waken at his usual hour with some slight paresis of the limbs only, and some hours may then elapse before the paralysis is complete.

More rarely attacks begin during the day and, in my experience, such are slow in onset or even of an abortive type, but Osler describes unconsciousness and also inco-ordination of the limbs as ushering in a diurnal attack.

By day more often there is a feeling of malaise, general fatigue and weakness which forces those affected to lie down, and as foreshadowing attacks by day, affections of character, irritability, emotionalism or erotic manifestations are sometimes present. It is to be noted that in women attacks are not infrequently associated with the menstrual periods.

Many of the attacks which occur by day are of an abortive type; one patient in my series had numerous such attacks. They may vary from merely a stiffness and weakness in the lower limbs to a slight paresis with weakened response of the tendon reflexes and slowing of muscular contraction. These abortive forms are usually dispelled by lying down for one or two hours with the application of additional clothing or heat.

In the fully developed attack the patient lies in bed with powerless

but not atonic limbs, unable to raise the head or to change his position in bed, and the latter disability in a long attack is to the patient about the most unpleasant feature. In the majority of cases the cranial nerves are not seriously affected, but it is not uncommon to find that there is some embarrassment of their function, so that coughing or sneezing may be impossible. Speech is more rarely affected and this is probably often due to paralysis of the expiratory muscles. Two patients in my series frequently suffered from such bulbar affections and both died as a result of this involvement. Paralysis of the palate has been described by Janota and Weber.

The paralysis is the primary feature and has the appearance of a peripheral or lower motor neurone lesion in that it is not of a spastic type and the deep reflexes are absent or sluggish.

Occasionally after having reached its maximum intensity, as a rule several hours after its commencement, the paralysis is diminished slightly and is then intensified before disappearing. The voluntary muscles are mainly affected, especially the muscles of the limbs; in the majority of cases the muscles of the lower limbs are first and most severely affected, and sometimes a paraplegia may be the whole manifestation of an attack. More rarely the upper limbs may be alone affected and even a hemiplegic distribution, or a monoplegia, may occur. In the most common form of attack, however, there is usually perfect symmetry in the involvement of muscles.

The muscles of the abdomen are usually affected in the ordinary form of attack, but on the whole the flexor muscles are less affected than the extensors, while in the more severe attacks the intercostals and accessory muscles of respiration are involved.

Although it is uncommon for urine to be passed during an attack lasting twelve to twenty-four hours, yet when the paralysis persists for two or three days urine is voided normally as the bladder becomes distended. A temporary anuria associated with profuse sweating has been observed, and Clarke describes cases in which micturition was difficult or impossible, as well as a case in which incontinence occurred; his experience, however, is very unusual. Erection, although usually absent during an attack, has, however, been described.

Though various paræsthesiæ occur as prodromata, the integrity of all forms of sensation is a feature of an attack. It is true that there is occasionally complaint of pain in the paralysed limbs during a seizure, but this probably results from the inability to move leading to the prolonged maintenance of the limbs in one posture, aggravated perhaps by the associated hypothermia and sweating.

Consciousness is absolutely unimpaired throughout the paralytic state and in the two patients in my series in whom death took place at the height of an attack consciousness was preserved till the end.

The occurrence of death during an attack is extremely rare; Holtzapple was able to collect six instances, including one personal case, the determining causes being paralysis of the respiratory muscles, cardiac dilatation and failure, or an inhalation bronchopneumonia.

The duration of the paralytic attacks varies from hours to days, but in general the duration of the attack is in direct proportion to its severity. The muscles first paralysed are usually the first to recover the power of movement. In general, once recovery commences the *restitutio ad integram* is rapid, but after recovery there is usually a feeling of fatigue, lassitude, or slight headache with a diminution in the activity of the tendon reflexes, and some writers have described several loose stools or even actual diarrhoea as occurring at this stage. Hyperexcitability of the facial nerve (Chvostek's test) has been found by Janota and Weber at the end of an attack.

It is claimed that certain of the paralytic attacks can be shortened by massage, induced sweating, purgation or by passive movements, but I have been unable to confirm this in my series, though certain of my patients have been able, like others recorded, to "walk off" threatened attacks by rising from bed when prodromata occurred and walking about for variable periods.

In addition to the paralysis there are also certain associated neurological phenomena, of which the most important is the disturbance in the electrical reactions of the affected muscles. Goldflam noted hypoexcitability of the affected muscles to the galvanic and faradic currents during an attack and even a partial reaction of degeneration. His findings as regards polar changes have not been confirmed by all those who subsequently reported cases of this disease, but in the majority of instances there has been a diminution or failure of response to the faradic current, and in many absence of response to galvanic stimulation also. In muscles partially paralysed the loss of electrical excitability is proportional to the degree of paralysis. Collier, however, while agreeing that in the paralytic attacks there is loss or diminution in the response to the faradic current, has found no change in the galvanic response.

In my patients in whom the electrical reactions were tested during a severe attack, no response was found to faradism or galvanism during the period of complete paralysis, while in the transient, brief, or abortive attacks slight or no diminution to the faradic current was found. In

the case of some standing already mentioned, where the leg muscles showed the consistence found in certain myopathies, there was a diminution in the response to the faradic current compared with that found in the rest of the body in the quiescent period between attacks

The tendon reflexes are absent during an attack, and as previously mentioned it may be some time after an attack before normal responses are obtained. In those who are severely affected by the disease as evidenced by the frequency of the attacks, there may occur a permanent loss of tendon reflexes; this was well-marked in my patient, J. W., whose attacks were very frequent over a period of years and whose father had also suffered from the disease and died in a paralytic attack. The knee-jerks are most commonly lost, but in the above instance the ankle-jerks were also absent and the arm-jerks on both sides were extremely sluggish. The disappearance of postural and pharyngeal reflexes in the later stages has also been described. Between attacks the patient's condition otherwise is absolutely negative both from a subjective and objective point of view, but very slight and abortive attacks are not uncommon, perhaps affecting only some groups of muscles in the lower limbs and necessitating only a brief rest before the patient is able to go about again.

Profuse sweating is common and as a rule is greatest at the full development of an attack, though rarely it has been described as reaching its maximum while recovery is commencing. Sleep is normal, even during attacks which last for some days, except for that discomfort due to inability to change the position; somnolence has been rarely noted as a prodromal symptom, and Fischl declares that sleep sometimes occurs as the equivalent of an attack.

In three cases described by Buzzard, a mother and two sons, the onset of the attacks so definitely occurred during a period of rest following active exercise that he was easily able to have attacks induced for his observation. In the case of the mother the onset was so fulminating that in the course of a few minutes she was unable to rise from a sitting or lying position; she had also a choking sensation during an attack and sometimes more definite respiratory embarrassment; in addition mastication and speech were only carried out with a certain amount of fatigue.

The sons were emotional and easily upset during attacks, and in one alarming signs of syncope occurred during the seizures. They were sometimes affected two or three times a day, but less severely than their mother; and recovery occasionally took place in half an hour

even when the muscles of all the limbs had been paralysed, with inability to sit up, slight bilateral ptosis, dysarthria, and absence of electrical response in the affected muscles. In one attack in which the patient following active exercise became unable to raise himself from a chair or his arm above his head, he was able, after only a period of ten minutes, to walk again, although with difficulty.

In addition to the diminution in the reflex response it is not uncommon to find in those patients who have suffered from recurring paralytic attacks for many years some permanent change in the muscles with or without persisting paresis. The muscles may have that fibrous or rubber-like consistency which one finds in certain of the muscular dystrophies, and even changes of a pseudo-hypertrophic nature have been recorded. Moreover cases of family periodic paralysis have been described in which other members of the family who had never suffered from periodic or any paralytic attacks presented the clinical picture of one of the muscular dystrophies. The association of family periodic paralysis with myasthenia gravis I have already described. Whether such changes indicate a co-existing muscular dystrophy, or a specific dystrophy associated with the muscular involvement in family periodic paralysis, we do not as yet know. In cases thus associated with dystrophy of muscles Janota and Weber found in the intervals between paralytic attacks a qualitative modification in the electrical excitability tending towards a myasthenic reaction, and in other cases reactions resembling those found in veratrinized muscle and in Thomsen's disease.

Atwood has noted a transitory albuminuria, and Schlesinger acetonuria during attacks. Several other writers having found indicanuria have stressed its presence as evidence of abnormal destruction of protein in the lower bowel and have blamed constipation as an exciting factor.

Dilatation of the heart has been described by Holtzapfel, Oppenheim, and by Janota and Weber in an attack along with weakness of the pulse, and slowing and arrhythmia of the latter have also been observed. Systolic murmurs have been noted in association with the dilatation, and the dilatation has been confirmed radiographically by Fuchs. Electrocardiographic tracings were taken by Janota and Weber both during and between the attacks. In one of their patients, when the vascular complex was normal between the attacks with a definitely positive T, they found accentuation but not enlargement of R in leads 1 and 2, with T diphasic and poorly defined. These findings are not in

favour of unilateral preponderance or of any affection of the conduction of ventricular action, but they do resemble the changes found by Rothberger in a patient showing a marked degree of vagotonia. Arterial hypertension has also been described.

Some affection of the digestive system is not uncommon during an attack. Diminution of appetite is usual, and eventually complete anorexia occurs, but sometimes, as in the prodromata, there is a craving for special articles of food, such as fruit and meat. Goldflam has described nausea and vomiting as accompaniments of attacks, but these are uncommon phenomena. From the diminution of muscle tone and of intestinal peristalsis constipation and flatulence are frequent. Enlargement of the liver with great thirst has been noted as well as the secretion of extremely thick saliva, but of all the digestive symptoms described anorexia and thirst are probably those most commonly found. Although the bowels are usually confined, in two of my patients in whom the attacks lasted four and two days respectively the bowels moved normally on their being carried to stool.

The blood picture was found by Wexburg to resemble that found in Graves' disease, while Goldflam noted a neutrophilia with eosinophilia, and Taylor a basophilia even reaching up to 51 to 57 per cent. As a rule, however, examination of the blood has shown no definite abnormality, and though a moderate lymphocytosis has been noted by some writers, we have no information as regards the time, in relation to meals, at which their examinations were made. The blood-sugar has been found by Janota and Weber to be a little above the normal figure, and the same authors along with Neustaedter note an increase in the height and duration of the blood-sugar curve after the ingestion of glucose, but without the occurrence of glycosuria. The diminution in the amount of the serum-calcium described is of interest in association with the cramp-like pains noted by some patients as prodromata, and with the occurrence of the Chvostek phenomena.

(4) *Diagnosis.*—A complete neurological examination during an attack should exclude hysteria, and investigation regarding familial nervous disease should in the majority of cases make clear the diagnosis.

The complete preservation of consciousness distinguishes family periodic paralysis from epileptic attacks, even from the rare paralytic type described by Higier.

Landry's paralysis, the transitory paralysis of myotonia, myasthenia gravis, and the paralysing form of vertigo described by Gerlier, need

only be mentioned in the consideration of differential diagnosis as in all of these there are other characteristic symptoms and signs.

Some writers have described the occurrence of the muscular dystrophies in the families of patients suffering from periodic paralysis, even the pseudohypertrophic form having been described. Thomsen's disease, or at least the presence of electrical reactions of a myotonic type, has been noted, while progressive muscular atrophy has also been recorded in association with the disease.

Only rarely have epileptiform seizures been described in addition to the attacks of paralysis, but there has been an association of family periodic paralysis with Higier's *épilepsie paralytique*. Migraine, urticaria and other conditions where an anaphylactic basis is thought probable, have also been described as associations, as have also certain psychical affections, and while tetany itself has not actually been found as an accompaniment of the paralytic state, yet the electrical reactions similar to those found in tetany, and a Chvostek's sign, have been noted.

DISCUSSION.

I attribute great importance to the association of migraine with paralytic attacks in the series of cases of family periodic paralysis recorded by Holtzapple, the largest series yet on record. Holtzapple observed in four generations of one family 17 cases of periodic paralysis. In this family also, 18 members suffered from periodic sick headaches of a definitely migrainous nature; 5 members suffered from such headaches associated with paralytic attacks, 14 had attacks of headache only, and 13 had attacks of paralysis only. The total number affected with either paralysis or headache was 32. Holtzapple believed the headache to be an equivalent of a paralytic attack. Although this association has not been noted by those who have since described cases of this disease, it has been present in two cases in my own series.

In migraine the influence of a deficient digestive function appears to be of importance. The affection of the digestive function by physical processes is generally admitted, and Cannon has shown experimentally that emotion plays an important role in the movement of the stomach, by demonstrating that peristalsis ceases whenever the animal shows signs of rage, distress, or even anxiety. Since mechanical stretching is the stimulus which produces contraction of plain muscle, such as that in the stomach and intestines, it follows that when the muscle is atonic, as is commonly the case in migraine, there is passive or flaccid distension

with abeyance of peristalsis, so that stasis and decomposition ensue, and the possibility of decomposition is further enhanced by the deficiency or absence of secretion of free hydrochloric acid in the stomach, a function also much influenced by psychic processes.

Alvarez has described cases in which fright or shock has caused for hours inhibition of the digestive processes in the stomach, while mental exhaustion, anxiety states and physical exhaustion, are similarly associated with cessation or impairment of gastric digestion.

In two of my cases of family periodic paralysis in whom fractional test meals were performed, disturbance of gastric function was evident; in one, achylia gastrica and deficient starch digestion were noted, and in the other, even at the end of two hours, digestion of starch had not taken place. In six cases of migraine thus investigated, I have found similar changes, and radiological examination showed atony, and on some occasions delay in the advance of the barium. Indicanuria, although not constant in these conditions, is occasionally found, and this suggests that intestinal decomposition is taking place as a result of the digestive deficiencies. As a result of deficient gastric digestion, abnormal metabolic products thus formed may not only produce the symptoms of a general toxæmia, but by their action either directly on the sympathetic system or by stimulation of the vasomotor nerves in the vessels, may cause changes in the central nervous system common to both diseases. Moreover, the possibility of absorption by the vagus of toxins from the stomach itself has also been described. Loeper, Forrestier and Tounet found in the trunk of the vagus tetanus virus and formol which has been administered by the stomach, and these they believed to have reached the nerve through minimal lesions in the gastric mucosa. These authors have also noted the presence of an increase in chlorides in the vagus during digestion, and moreover have found pepsin in the cerebrospinal fluid, while tetanus toxin administered by the stomach has later been identified in the medulla, but not in the brain itself.

In the further consideration of the relationship between family periodic paralysis and migraine, we know that in migraine paralysis may occur, not only of the ocular muscles, but sometimes of an arm, and even more rarely of a hemiplegic distribution. Bulimia is a common precursor in both conditions, and although sufferers from migraine usually go to bed on the day preceding an attack with no warning that it is impending, yet, as in family periodic paralysis, it is most common for them to waken with the headache and feeling of

lethargy and intoxication in the morning. While in family periodic paralysis the attack is said to supervene during sleep or in a state of rest following a period of muscular activity, in migraine worry and mental exhaustion are more common as exciting factors than physical exhaustion.

Our ignorance of the pathology of epilepsy makes it of little value to contrast the attacks of idiopathic epilepsy with those of familial periodic paralysis, but it is interesting to consider certain factors common to both conditions. These are the influence of heredity, the cyclical nature of the attacks, which are associated in some patients with dyspepsia and evidence of intoxication, while in others they are associated with endocrine dysfunction, and, if infrequent, may only occur in association with menstruation. In general their occurrence can often be related to some metabolic disturbance associated with an affection of the vegetative nervous system. Moreover, a certain number of those who suffer from migraine in childhood or adolescence subsequently develop epilepsy, while a history of migraine and of other neuropathic conditions among the relatives of epileptics is not uncommon.

In spite of wide difference in the manner of onset and duration of the attacks, yet narcolepsy, the pathology of which is also still unknown, calls for consideration in respect of the analogies presented by the cataplectic seizures. The attacks of cataplexy, incited usually by an emotional state, and of a duration measured in seconds, are of an atonic flaccid nature, and in the attack personally observed by Kinnier Wilson reflex activity was lost and a unilateral extensor plantar response was present until two minutes after the recovery of power, while a temporary disturbance in the electrical reactions has also been described. Although these fulminating palsies present a picture similar to that developed, after hours or days, in periodic paralysis, yet there is no familial neurological taint and no evidence of intoxication, and while agreeing with Adie that narcolepsy and cataplexy are probably both of the nature of inhibitory phenomena, I do not consider that this theory is applicable to familial periodic paralysis.

It is difficult to believe, however, that in family periodic paralysis the presence of some toxin in the blood could alone account for the attacks of paralysis, which are the main features of the malady and which may last for some days, especially as we know that during the whole of the attack it is usual for the excretory functions to be inactive, so that the elimination of such a circulating poison is unlikely. Moreover, in intoxications affecting the lower motor neurones the peripheral

muscles are first affected, and volitional movements are diminished or lost for a considerable time before the electrical reactions are impaired, whereas in family periodic paralysis the response of the muscles to voluntary and electrical stimulation disappears *pari passu*, and following even complete paralysis the recovery to volitional and electrical stimuli is equally quick. Those facts, as well as our knowledge that muscular exertion or exhaustion is not a constant predisposing factor in all those who suffer from the disease, enable us to oppose those theories which have been advanced that normal products of muscular activity either in excessive strength, or acting in the presence of lowered body resistance, can cause the paralysis of the muscles in this disease. The suggestion that a poison with a seat of selection in muscular tissue similar to curare is the cause of the paralysis is opposed by our knowledge that the muscles of curarized animals show no electrical changes. It appears therefore improbable that this disease is caused by a general intoxication *per se*, and we must therefore consider the possibility of some abnormality in the muscle tissue itself, which may be unduly sensitive either to a general intoxication or to the local metabolic changes which result from prolonged or extensive muscular activity.

We know that relatives of those who are affected with family periodic paralysis have been found to suffer from various forms of the muscular dystrophies, and we know also that those who have suffered from the periodic paralytic attacks for some years may themselves exhibit weakness and the physical changes characteristic of the dystrophies, so that it is not improbable that some abnormality of the muscular tissue is a feature in those who suffer from family periodic paralysis.

When we consider that in some patients the attacks of paralysis have definitely followed severe exercise, or have taken place during muscular repose, as during sleep, following upon the general fatigue of a hard day's work, we are led to wonder whether there may not be some interference with the circulation of the blood or lymph preventing the removal of the products of muscular metabolism.

As regards the circulation of the blood, it may be noted that in some cases, and especially in those I have personally described, cold has been a definite exciting factor, and may to some extent have been responsible for an inadequate circulation in the extremities which are the most frequently affected parts of the body, and may thus have interfered with the removal of the results of muscular activity, and as I already postulated a stimulation of the vasomotor system by toxins of

a gastro-intestinal origin, interference with the circulation may also take place from this cause.

The lymphatic circulation is, however, much more dependent on muscular contraction, and since the attacks most commonly commence during a period of rest or sleep following muscular activity, it is possible that the accumulation in muscle of products of its metabolism may be sufficient to cause changes in its substance which can affect its function of contractility. Moreover, during sleep respiration is more shallow and the blood-pressure is lower, so that the circulation of blood and lymph is further depressed.

Certain points noted in the disease appear to support such theories. Firstly, some patients on becoming aware of the onset of an attack are able, as they themselves say, "to walk it off" by getting up while the limbs are still only stiff and slightly paresed, moving them forcibly and then walking about, though it is to be noted that such attempts more often delay the development of a complete attack than actually abort it. The above theories may also account for the escape of the diaphragm, as the incessant activity of this muscle in voluntary respiration, and even during sleep, would prevent any stagnation of lymph in its substance; similarly the fact that the muscles supplied by the cranial nerves are infrequently and incompletely paralysed may be due partly to the fact that these muscles are in a state of some activity even when the muscles of the body in general are at rest, and the position of those muscles, above the junction of the lymphatic and venous systems, allows the effect of gravity, even while in bed, to aid their lymph return.

The fact that the muscles in an attack are not hypotonic but have a firm feeling, without there being any suggestion of spasticity, supports to a certain extent the view that the excessive lymph formed as a result of muscular activity remains and perhaps forms abnormal combinations in the muscle tissue, thus causing the firm consistence or induration in attacks, and also the permanent changes found in the muscles of those who have suffered from many attacks over a period of years. The fact that the muscles, in what is apparently a flaccid palsy, show no decrease or alteration in tone is of interest, and it is to be noted that in hypotonia found in other clinical states no definite alteration in the electrical reactions of the hypotonic muscles is to be found.

Although interference with the circulation of both blood and lymph may be present, and although it is possible that such changes could interfere with the muscle function of contractility and maintain a state of paresis, yet I feel that the paralysis is fundamentally due to the

presence of a constitutional defect in the muscle; and we can, I think, obtain confirmation of such a possibility from the consideration of certain hereditary tissue defects.

For the purpose of my thesis I would draw attention to one of the dystrophies, namely dystrophia myotonica, in which there is an indication that the neuro-muscular defect may be only part of a general constitutional abnormality. The condition is familial and usually first manifests itself about the age of twenty, but while it may be directly transmitted as a rule through males, yet more frequently a latent tendency may be traced through various relatives by evidence of bodily dyscrasias which are a feature of the disease. Of these cataract is most common, but changes in the thyroid gland, premature baldness, and testicular atrophy are also frequent, although it is to be noted that sexual life is usually normal until the onset of the disease. Other occasional findings are a relative lymphocytosis, increased irritability of the facial nerve, and most constantly vasomotor disturbances, especially cyanosis and coldness of the extremities.

In family periodic paralysis, in which there is the development of a characteristic syndrome in member after member of a family at about the same period of life, we find something in common with dystrophia myotonica, and although there are specific outstanding features in both conditions, yet it is evident that the basis in both is an abnormal constitution or diathesis.

From a comparison of family periodic paralysis, with migraine and epilepsy, I have indicated that instability of temperament and a liability to periodic intoxications are features common to the three conditions, yet, while in familial periodic paralysis the muscular defect is not of the nature of a true abiotrophy, in that the condition is not always progressive and may even in the latter years pass away, I nevertheless consider that there is some inherent muscular deficiency upon which a periodic disturbance of the vegetative system, with associated intoxication, acts to produce the paralytic attacks.

SUMMARY.

Six cases of familial periodic paralysis are described in three generations of one family, and the histories of families previously recorded as suffering from this disease are reviewed.

The condition tended to develop about the age of 17 or 18 years in each member of the family, and in some patients who have suffered from paralytic attacks for years there was a development of permanent

muscular weakness and rarely the picture of one of the muscular dystrophies; the occurrence of muscular dystrophies in other members of the families, who were not themselves affected by periodic paralysis attacks, is also described.

The condition is compared with migraine, epilepsy, and certain heredo-familial degenerative diseases.

It is considered that two factors are concerned in causing the attacks of paralysis.

(1) An abnormal constitution of diathesis in which there exists, in patients with a neuropathic inheritance, a condition of disequilibrium of the vegetative nervous system with evidence of periodic intoxication associated with abeyance of the digestive function and abnormal metabolism at the time of the attacks.

(2) Some abnormality in the muscles themselves.

It is believed that the attacks of paralysis are caused by the low resistance of the defective muscle to abnormal metabolic products present during the periods of intoxication, while it is probable that interference with the blood and lymph circulation in the muscles, which results from the disturbance of the vegetative system, is a contributory factor.

REFERENCES.

- ADIE, W. J. *Brain*, 1926, **49**, 257.
 ADIE and GREENFIELD. *Ibid.*, 1928, **48**, 73.
 ATWOOD. Stair's "Organic and Functional Nervous Diseases," 1918.
 ALLBUTT and ROLLESTON. "System of Medicine," London, 1910.
 ALVAREZ. "The Mechanics of the Digestive Tract." New York, 1928.
 BARRÉ and DRAGANESCO. *Rev. Oto-Neuro-Ocul.*, 1926, **4**, 376.
 BARUK and MEIGNANT. *L'Encéphale*, 1929, **24**, 466.
 BUZZARD, E. F. *Lancet*, 1901, **2**, 1564.
 CANNON. *Amer. Journ. Physiol.*, 1905, **13**, 22.
 CAVARRÉ. Quoted by HOLTZAPFLE.
 OLARKE. Allbutt and Rolleston's "System of Medicine," London, 1910.
 COLLIER. "System of Medicine," Ed. Price, London, 1930.
 COLLINS. *Journ. Nerv. and Ment. Dis.*, 1898, **24**, 745.
 DONATH and LUKATEL. Quoted by BUZZARD.
 FUCHS. Quoted by JANOTA and WEBER.
 FISCHL. Quoted by BARUK and MEIGNANT.
 GARDNER. *Brain*, 1912, **35**, 242.
 GETTINGS and PEMBERTON. Quoted by HUNTER.
 GIBSON, MARTIN and BURLL. Quoted by HUNTER.
 GOLDFLAM. *Zetschr. f. klin. Med.*, 1891, **19**, 240.
Idem. *Deutsche Zetschr. f. Nervenheilk.*, 1896, **7**, 1.
 GOWERS. "Diseases of the Nervous System," London, 1899.
Idem. "Epilepsy and other Convulsive Diseases," London, 1881.
Idem. "The Borderland of Epilepsy," London, 1907.
 GUILLAUME. "Vagotonies, Sympathicotones, Neurotonies," Paris, 1925.

- HOLTEAPPLE. *Journ. Amer. Med. Assoc.*, 1905, **45**, 1224.
HUNTER. "Creatine and Creatinine," London, 1928.
JANOTA and WEBER. "Die paroxysmale Lähmung," 1928.
LENNOX and COBB. *Medicine*, 1928, **7**.
LIVING. "Migrain, Sick Headache and Allied Disorders," 1873.
MACLAIRE. *Journ. Nerv. and Ment. Dis.*, 1925, **61**, 44.
MOUZON and TURPIN. Quoted by COLLIER.
NEUSTADTER. *New York State Journ. Med.*, 1922, **22**, 65.
OPPENHEIM. "Lehrbuch der Nervenkrankheiten," Berlin, 1928.
OSLER and MACCRAE. "System of Medicine," Philadelphia, 1928.
POWIS and ROPER. Quoted by HUNTER.
RICH. *Med. News*, 1896, **15**, 210.
ROTHBERGER. Quoted by JANOTA and WEBER.
SINGER and GOODBODY. *Brain*, 1901, **24**, 257.
SCHMIDT. "Die paroxysmale Lähmung," 1919.
SCHLESINGER. *Wien. klin. Wochenschr.*, 1905, **18**, 323.
SPRIGGS. *Quart. Journ. Med.*, 1908, **1**, 63.
TAYLOR. *Journ. Nerv. and Ment. Dis.*, 1898, **25**, 637.
TISSOT. *Encyclopédie des Sciences méd.*, 1840.
TROUSSEAU. "Clinique médicale."
WESTPHAL. *Berl. klin. Wochenschr.*, 1885, **22**, 489.
WILSON, S. A. K. "Modern Problems in Neurology," London, 1928.

ATROPHY AND DEGENERATION IN THE MUSCLE SPINDLE.¹

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THE spindles of skeletal muscle are structures receiving both dorsal-root and ventral-root innervation. They have, therefore, presumably both sensory and motor function. Hence, for study of the trophic dependence of tissue on innervation, the spindles afford a unique object.

Incomplete and conflicting evidence still obscures the condition of the spindle in the atrophy and degeneration of muscle consequent on denervation. In his pioneer work on the anatomical constitution of the nerves of muscle, Sherrington reported (1894) that the spindles remained intact when the bulk of a muscle was altered almost beyond recognition. His animals, cats, survived sciatic section five months. Horsley confirmed Sherrington in 1897; but in the same year Batten published his much more extensive studies. He examined the spindles in various pathological states of man and following peripheral nerve lesions in cats. In the latter he found the spindle muscle fibres atrophied in proportion to the time elapsing after operation. Later, Boeke (1916) again reported such degenerative changes, the result of peripheral nerve lesion. However, the only data on the trophic relations of the nerve roots to the spindle were presented by Onanoff, in 1890, thus antedating Sherrington's experiments. On the slightest of evidence, Onanoff concluded that the spindle was in trophic and motor dependence on the anterior horn cells.

Thus the problem of the trophic relationship of the muscle spindle to the nervous system opens itself to attack in two stages. First, the reaction of the spindle to peripheral nerve lesion must be definitely established. Then, if the spindle shows atrophic and degenerative changes, the responsibility of the various components of peripheral

¹ This study was commenced while the author was a Fellow of the Henry Strong Denison Medical Foundation.

innervation, the dorsal and ventral root components, and possibly the sympathetic, for maintaining the normal state of this complex sensori-motor organ, must be analysed.

I.—THE REACTION OF THE MUSCLE SPINDLE TO PERIPHERAL NERVE LESION.

Material and methods.—Peripheral nerve lesions were produced in six young adult cats. The brachial plexus was exposed, under ether anaesthesia, from the axilla to the elbow. The component nerves (radial, median, ulnar, musculo-cutaneous, medial external cutaneous) were isolated. One to three centimetres of each nerve was excised, and the cut ends turned back and tied to the trunk. In order to eliminate sympathetic nerve fibres which might travel to the periphery along the blood-vessels, the stellate ganglion was removed in one of the animals (S VIa). From two more (S VIc, S VId) this ganglion and the entire cervical sympathetic chain were removed. The stellate ganglion was reached through the vertebral end of the first intercostal space by entry below the scapula. The cervical sympathetic cord and ganglia were exposed by an incision the length of the neck.

Pairs of animals, one with simple brachial plexus section and the other with the added sympathetic denervation, were allowed to survive four, six and twelve months. Because of these long survival times, the possibility of regeneration had to be considered. For the sympathetic lesions, this was not a problem; the post-ganglionic cell bodies were gone. Furthermore, the persistence of vasomotor and sudomotor paralysis was evidence that sympathetic nerve fibres were not present. The somatic nerve fibres gave signs of regenerating only in the two animals surviving operation a year. In one of these (S VId), at the time of death the reaction to pin-prick had returned in a strip extending down the anterior border of the forearm, but not on to the wrist. In the second (S IIe), so rapid was the return of sensibility that in the twelfth, and again in thirty-sixth week, the brachial plexus had to be re-exposed, the proximal stumps of the nerves located and an additional length of each removed. There was at no time, however, in any animal a recovery of lost motor function. Subsequent examination of the histological preparations confirmed the completeness of the denervation for all the cats except one. In this animal (S IIb), killed four months after operation, a small number of nerve fibres in an early stage of regeneration were found distributed through the interosseous muscles. About one-half of the spindle capsules contained nerve fibres, though

no definitive equatorial or polar endings were formed, and a smaller proportion of the old motor plaques of the extrafusal muscle fibres also received nerve fibres.

When the time of survival allotted a cat had expired, the animal was killed with ether, the aorta cannulated, and two litres of physiological salt solution perfused through the blood-vessels. This was followed by one or two litres of the fixative, 20 per cent. neutral formalin. After the material had stood in the fixative six months or more, specimens for histological study were removed and put through a modified Bielschowsky silver technique. The entire fifth interosseous muscle and the lateral slip of the fourth were cut serially, longitudinally at 15 μ . Cross-sections were made at 10 μ , from the middle of the belly of the remaining three slips of the fourth interosseous muscle. Specimens from the side of operation and from the normal side were treated alike in each case.

Control.—The two muscles, the fifth and fourth interossei, were selected for concentrated study, because it was thought that in this way a standard might be established both for the number of spindles present in the muscle and for their form. Thus, ten normal fifth interosseous muscles yielded an average of nineteen spindles each, with a maximum of twenty-four and a minimum of fourteen. For the lateral slip of the fourth interosseous muscle, the average was five spindles; the range, two to nine. Curiously enough, there seemed to be little correspondence between the number of spindles in the same muscle from opposite sides. For example, in one animal (S II f), the left fifth interosseous muscle contained twenty-two spindles; the right, fourteen.

A variety of spindles were found in the cat's interosseous muscles. There were simple spindles, and compound; spindles with a short equatorial region, and those in which this structure took in the greater portion of the spindle. There were spindles with small tight capsules, and with voluminous capsules; spindles with two intrafusal fibres at a maximum, and spindles with twelve. But all these are quantitative variations on one spindle pattern which has been repeatedly described by a series of investigators before and since Sherrington (1894). Plate III shows the typical appearance of the normal spindle in longitudinal and cross-section.

The manner of innervation of these muscle spindles has also been well expounded, most recently by Hinsey (1927) and by Hines and Tower (1928). To the conclusions arrived at in these papers the present study has nothing to add, except a conviction that the rich

confusion of nerve fibres at the spindle poles and in the capsule has not yet been thoroughly analysed.

Observations.—Following peripheral nerve lesions, the muscle spindles atrophy and degenerate. Moreover, the reaction of the intra-fusal muscle fibres is quite in proportion to the reaction of the extra-fusal, and of the same nature. For both, the duration of the lesion is the chief factor. Thus, after four months' denervation atrophy was far advanced. This was attested grossly by the diminished bulk of the muscle. Microscopically, the signs of atrophy were also largely quantitative. The muscle fibres were thinner and shorter; the brilliance of striation subdued. But at four months evidences of actual degeneration were scanty. Even after six months the picture was still predominantly one of atrophy, although large areas of degenerating muscle were now to be found. Throughout this material there was no difficulty in finding the spindles. They did not, it is true, stand out in the manner described by Sherrington and by Horsley. Indeed, connective tissue had so bound the capsule to neighbouring structures on the outside, and to the axial bundle within, that the spindles were much less conspicuous than normal, the more so since the striking nerve fibres and endings were also wanting. However, a complement of spindles well above the lower limit set by the control material was always found. Furthermore, in cross-sections there was no difficulty in making out a number of intrafusal muscle fibres also up to the normal.

After a year of denervation, however, degeneration was far advanced. Well-preserved extrafusal muscle fibres were to be found only here and there in the mass of fibrous tissue. And although a sufficient number of spindles were located in the interosseous muscle from the side of lesion (S IIe, 18; S VIId, 22), this was only by vigilant search. Within the individual spindle, recognized perhaps by a fragment of the equatorial nuclear aggregation within a thickened capsule (fig. 4a), degeneration had frequently gone so far that no estimate of the number of intrafusal fibres could be arrived at. And the polar regions of these spindles (fig. 4b) had become indistinguishable from the surrounding fibrous tissue. Curtailed thus in length, enclosed in a narrowed and thickened capsule, the spindles were, indeed, almost lost in the fibrosing mass that had been muscle.

The two processes—atrophy and degeneration—are consecutive, and more clearly distinguished by dictionary definition than in fact. For the extrafusal muscle fibre, the stages of degradation may be briefly out-

lined. The nuclei reacted first. They became large and oval, and more deeply embedded in the fibre. Instead of the multiple small nucleoli characteristic of sarcolemma nuclei, there was a single large nucleolus, or none. The cross-striation faded, the light band becoming wider and the dark band paler. Fracturing along the line of cross-striation was common. At the same time the longitudinal disposition of the myofibrillæ became emphasized, especially toward the ends of the fibres, and along these lines the fibres also split. And preceding and accompanying these changes there was the progressive reduction in the size of the fibre which is the chief feature of atrophy.

Final destruction of the muscle tissue followed either of two courses. There was an acute process of degeneration, more conspicuous in the first half-year after the lesion than later. The entire length of a fibre, losing all semblance of internal structure, was reduced to a vesicular or vacuolated mass in which the swollen nuclei were quite irregularly disposed. The sarcolemma lost its sharp straight outlines and the contents of the fibre collected in lumps. At many points the sarcolemma seemed to break. This process, especially when it affected a group of muscle fibres, was attended by the infiltration of numbers of round cells, chiefly of a mononuclear type. At a later period, six months or a year after denervation, this acute process of degeneration was reinforced by a second degenerative process. Beginning toward the ends of a muscle fibre, the cross-striation disappeared and the myofibrillæ stood out as discrete strands. The nuclei, caught now between the fibrils, became extraordinarily elongated and the sarcolemma less clearly delimited fibre from fibre. Indeed, a year after denervation, it was usually impossible to discriminate the individual fibres of a fascicle cut in cross-section. Gradually, by these changes, the muscular tissue was reduced to a fibrous state. The muscle fibre became, to all appearance, a tendon filament, and the whole muscle a broad, flat tendinous mass.

All the features of atrophy and both processes of degeneration just described for the extrafusal fibre were exhibited by the intrafusal fibres as well (Plate IV). In the polar regions, especially, the reactions were identical. The muscle fibres first became thinner and shorter. Their nuclei, already central and oval, swelled. The cross-striation regressed and the myofibrillæ stood out prominently. Some fibres showed vesicular degeneration, but the majority were involved in the fibrotic process. Fig. 3b illustrates both degenerative changes in two fibres of the proximal pole of a spindle. In the upper fibre the nuclei are swollen and the cytoplasm vacuolated; in the lower fibre the nuclei are drawn

out between the longitudinally disposed fibrillæ. At the equatorial region, because of its peculiar structure, the picture was somewhat modified. The nuclei, already round, seemed first to swell, then to shrink. Their smoothness and sharpness of outline was lost, and they became confluent (figs. 3*a* and *c*). The nucleolus, an intense black spot in the centre of the normal equatorial nucleus (fig. 1*c*) disappeared. And the numbers of the nuclei were greatly diminished (compare figs. 3*c* and 4*a* with 1*c*), seemingly by the process of nuclear fusion. Furthermore, the intrafusal fibres also lost their clarity of outline, so that frequently the cytoplasm of the axial bundle formed a mass in which individual fibres were not distinguishable except by the cords of fused nuclei (fig. 5*b*).

The equatorial region of the spindles was the most resistant to complete degeneration of all the parts of the muscle. However, occasional fibres showed vesicular disintegration of the scanty cytoplasm between the nuclei. And fibrosis, though less obvious, was quite general. This last reaction may be seen in figs. 3*a* and *c* in the best preserved spindle of a fifth interosseous muscle after one year of denervation. In concert with the reduction in size and number of the equatorial nuclei, there was every indication that in the course of time the fibrous transformation would have been completed, as indeed it very nearly was in the spindle shown in fig. 4*a*. Certain it is, however, that were fibrosis complete, the criterion for identifying a structure as a spindle would be destroyed. Although it is not likely that many spindles had suffered this fate, for an average number were still recognizable, it is probable that many individual fibres of the axial bundle had taken this course. For in spindles much altered, but in which fibres were still discernible, these were few in number (fig. 4*a*).

The connective tissues of the spindle reacted to denervation in common with the connective tissues of the remainder of the muscle. In neither case, however, was connective-tissue proliferation excessive until the final stage of fibrotic degeneration had been reached. The spindle capsule first increased slightly in thickness, often at the expense of the periaxial space. Bands of connective tissue, perhaps the original delicate conveyors of nerve fibres, bridged this space. At the poles the capsule closed down gradually on the intrafusal bundle. Thus the periaxial space was encroached on from both ends and narrowed at the middle. Later, the fibrous connections between the capsule and adjacent structures also multiplied. Finally, the capsule became indistinguishably merged in the surrounding fibrotic mass, and a short length of

grossly atrophied or degenerating muscle fibres in a much curtailed periaxial space was all that remained of the spindle. Figs. 4a and b show, not indeed the final stage of this process, but the last stage giving sufficient contrast of muscle fibre and fibrous tissue for demonstration photographically.

These observations on the results of peripheral nerve lesion apply to the entire group of six cats. Section of the brachial plexus completely denervated the tissues examined. The addition of sympathetic ganglionectomy to this lesion made no appreciable addition to the functional or structural losses in the fore-limb. If sympathetic nerve fibres are sent to the fore-limb by way of the blood-vessels, without an intermediary course in the peripheral nerves, their number is so exceedingly few and their influence so slight that they eluded detection in this study.

Following peripheral nerve lesion, therefore, and in the absence of regeneration, the spindles of skeletal muscle atrophy and degenerate. Furthermore, in the muscles selected for this study, atrophy and degeneration develop along the same lines and with about equal slowness in both extra- and intrafusal muscle. One aspect of this process which was most interesting was the convergence of the various muscle tissues to a common form, with the loss of characterizing features. First, the extrafusal muscle approximated the type of the polar regions of the intrafusal fibre; narrow fibres, central nuclei, coarse striation with equally wide light and dark bands. Later, by loss of striation and increase of nucleation, both came to resemble, sometimes to a confusing degree, the now dispersed equatorial region. The end-product of degeneration for all three tissues was the same—fibrous tissue. It was striking, moreover, that in these processes of decay the equatorial region, which is least differentiated as muscle, retained its character longest. For it was by coming upon equatorial aggregations of nuclei, much reduced to be sure, that the spindles were recognized, in many instances, in an otherwise completely fibrotic mass.

One cannot but speculate, if after a year of denervation extra- and intrafusal muscle are still fragmentarily recognizable as such, how long does muscle tissue maintain its character? And what is more important, should nerve fibres return, for how long a period is the tissue sufficiently preserved to resume its original form and function? Those muscle fibres affected by vacuolar degeneration are obviously completely broken up and removed. But the fibrous process is less destructive. In a region of muscle which on first glance seems completely converted

into tendon, on close inspection faint lines of cross-striation may be observed. Furthermore, the original muscle nuclei and myofibrils, though altered, are still present. And in the spindles vestiges of equatorial aggregation are most persistent. So long, then, as trace of their original structure remains, are these tissues, under proper stimulation, capable of redifferentiation and resumption of function? Or are they, as it were, mere ghosts, incapable of resurrection?

II.—THE TROPHIC RELATIONS OF THE COMPONENTS OF INNERVATION TO THE MUSCLE SPINDLE.

The fact has been established that the muscle spindles atrophy and degenerate following peripheral nerve lesion. In order to demonstrate how the components of the peripheral nerve share the responsibility for maintaining the trophic state of the spindle, the three components of such a nerve were now eliminated in turn, each in a group of animals.

The ventral roots, C_8 to T_2 inclusive, were cut on the right side in three cats. By opening the spinal canal, the roots were exposed as they pass laterally to form a spinal nerve. The dorsal roots were gently pulled aside, the ventral roots picked up, clamped and two or three millimetres of the root excised. All these procedures were performed extradurally. The animals were allowed to survive four, six, and twelve months. At the expiration of these intervals they were killed and fixed by injection; and histological preparations were made in the manner described for the peripheral nerve lesions.

The effect of ventral root section on the spindle was characteristic. At the polar regions, atrophy and degeneration developed as in the extrafusal muscle of the same specimen, or as after peripheral nerve lesion, and progressed at approximately the same rate (figs. 6*b*, 7*a* and *c*). The equatorial region, on the other hand, was very much less affected (figs. 6*c* and 7*b*). Degenerative changes seemed, indeed, to be confined to the poles.

At the poles the muscle fibres first became thinner and their nuclei swelled. In animals killed after six months, the cross-striation was noticeably fainter. Connective tissue had begun to obliterate the periaxial space, and at the ends of the spindle fibrous transformation had begun to curtail the length. Occasional fibres, not many, showed vesicular degeneration, and here round cells might be found inside the spindle capsule. After a year of denervation the process of converting the polar regions of the spindle, capsule and muscle bundle into fibrous tissue had progressed far. The majority of the intrafusal fibres showed

vacuolation and segmentation of the cytoplasm with a complete loss of cross-striation and, commonly, of longitudinal fibrillation as well. Figs. 6*b* and 7*a* and *c* illustrate these changes. Uncomplicated fibrous transformation was less common, although the upper fibre of fig. 7*a* shows this process, in contrast with the extreme vacuolation of its lower companion. The over-all length of the spindles was much reduced by shortening at the poles, though the equatorial regions were apparently of normal length (compare fig. 6*a* with 1*a*). This process had gone so far, indeed, in a few spindles that the recognizable portion consisted only of equator.

Standing out from the mass of atrophic or degenerated extrafusal muscle, the equatorial regions were most conspicuous. Enclosed often in much dilated capsules (fig. 6*a*), they were striking objects and seemed to have lost nothing of their normal appearance. On close inspection, however, the fibres composing the intrafusal bundle were perceptibly atrophic. They were thin (fig. 7*b*), and in cross-section the cytoplasm around and between the nuclei was obviously reduced in amount. Yet the individual fibres retained their clarity of outline; the sarcolemma was intact. On the other hand, the nuclei composing the equatorial aggregation appeared normal in every respect. They were round, clear-cut, never confluent, and the nucleoli were typically small and sharp (fig. 6*c*). Furthermore, the arrangement of the nuclei in rows was not disturbed, nor was their number appreciably diminished. The connective tissue encasing the axial bundle seemed slightly increased, but there was no evidence of fibrosis in any part of the muscle fibres bearing nerve fibres. Both the equator and the variably long regions of accessory sensory innervation—the regions where flower-wreath and club endings occur—seemed to be protected from fibrotic degeneration, and the transition from this region to the poles was often, after a year of denervation, very striking. Against the hazard of vacuolar degeneration, however, the presence of nerve fibres did not afford complete protection. This process, which often affected only one or two of the fibres of an axial bundle, penetrated even into the region of equatorial aggregation, though considerably less violently.

In contrast to the differential reaction of the parts of the intrafusal muscle bundle, the capsule of the spindle reacted as a whole. In animals subjected to denervation of four months, when the muscle fibres were still little altered, the capsule commonly appeared thicker from end to end. Heavier connective-tissue strands bound the capsule to adjacent structures and traversed the space between the capsule and the intra-

fusar bundle. In later stages this process completely obliterated the periaxial space at the poles. But at the equator the capsule, while thickened, frequently also became much dilated (fig. 6a). Veins, lymphatics and capillaries, particularly those of the spindle, often showed a similar dilatation (figs. 6a and b), perhaps a mechanical result of the atrophy of the surrounding and supporting muscular tissue.

The dorsal root ganglia, C₆ to T₂ inclusive, were removed on the right side in another series of three cats. The spinal canal was opened laterally as far as the intervertebral foramina. The root ganglia were freed from the ventral roots and excised without opening the dura. Subsequent histological examination of serial sections of these lesions showed that the ganglia were completely removed by this operation, no single cell remaining. However, the operation always entailed slight injury to the superficial layer of ventral root fibres (Tower, 1931). The three animals of this series were also allowed to survive four, six and twelve months. They were then killed and histological preparations were made in the usual way.

The reaction of the spindle to removal of the dorsal root ganglia was in striking contrast to its reaction to ventral root section. In the first place the capsule responded slightly or not at all to the lesion. It became, perhaps, somewhat smaller in diameter and thicker in the region where the bulk of sensory fibres and endings had been removed (fig. 8a), but there was no general thickening. The polar regions of the intrafusar muscle bundle likewise seemed unaffected. The muscle fibres were of good size; the nuclei elongated, perhaps unusually so; the cross-striation, intense and clear-cut (figs. 8b and d). Nerve fibres were present in the usual profusion at the poles, and endings of a very simple motor plaque type were occasionally found.

At the equator, however, the intrafusar muscle bundle exhibited extraordinary modification. Not very noticeably after four months, but quite clearly six months after lesion, the equatorial aggregation had altered. No longer were the nuclei arranged in compact rows, almost filling the sarcolemma. Around and between the nuclei cross-striated sarcoplasm had appeared. By the end of a year of denervation, the volume of cross-striated muscle substance surrounding the equatorial nuclei greatly exceeded the volume of the nuclei (most clearly shown in cross-section in fig. 9a). The nuclei, in turn, had become much smaller. And instead of being round and sharply outlined, they were now polygonal or square, or in spindles showing the most intense reaction, elongated and confluent as after peripheral nerve lesions (compare figs. 8c

and 3c). At the same time the muscle fibres became straighter of outline. All these features are illustrated in figs. 8a and c. In short, the unique characteristic of the equatorial region, the aggregation of nuclei, was in process of being obliterated, and the region was being converted to the structure of the adjacent polar regions of the spindle.

The sympathetic component of innervation was eliminated on the right side in two cats. From one animal, only the stellate ganglion was removed. This animal was then allowed to live four months. In the second animal, which survived operation one year, the stellate ganglion and cervical sympathetic cord and ganglia were taken out. Both operations seemed to be equally complete in depriving the fore-leg and paw of sympathetic fibres and function.

In contrast with the striking and characteristic results of excluding dorsal and ventral root components from spindle innervation, sympathetic denervation was without perceptible effect. Even so long as one year after the operation, the intrafusal muscle fibres seemed unaltered in any respect. The size, nuclei and striation were quite as in the control material (compare figs. 10a, b and c with 1b, c and d). Nor was the capsule appreciably thicker or thinner. Furthermore, it could not be detected that the number of nerve fibres going to the spindle was at all diminished. Indeed, so far as the spindle was concerned, the sympathetic lesion was inconsequential.

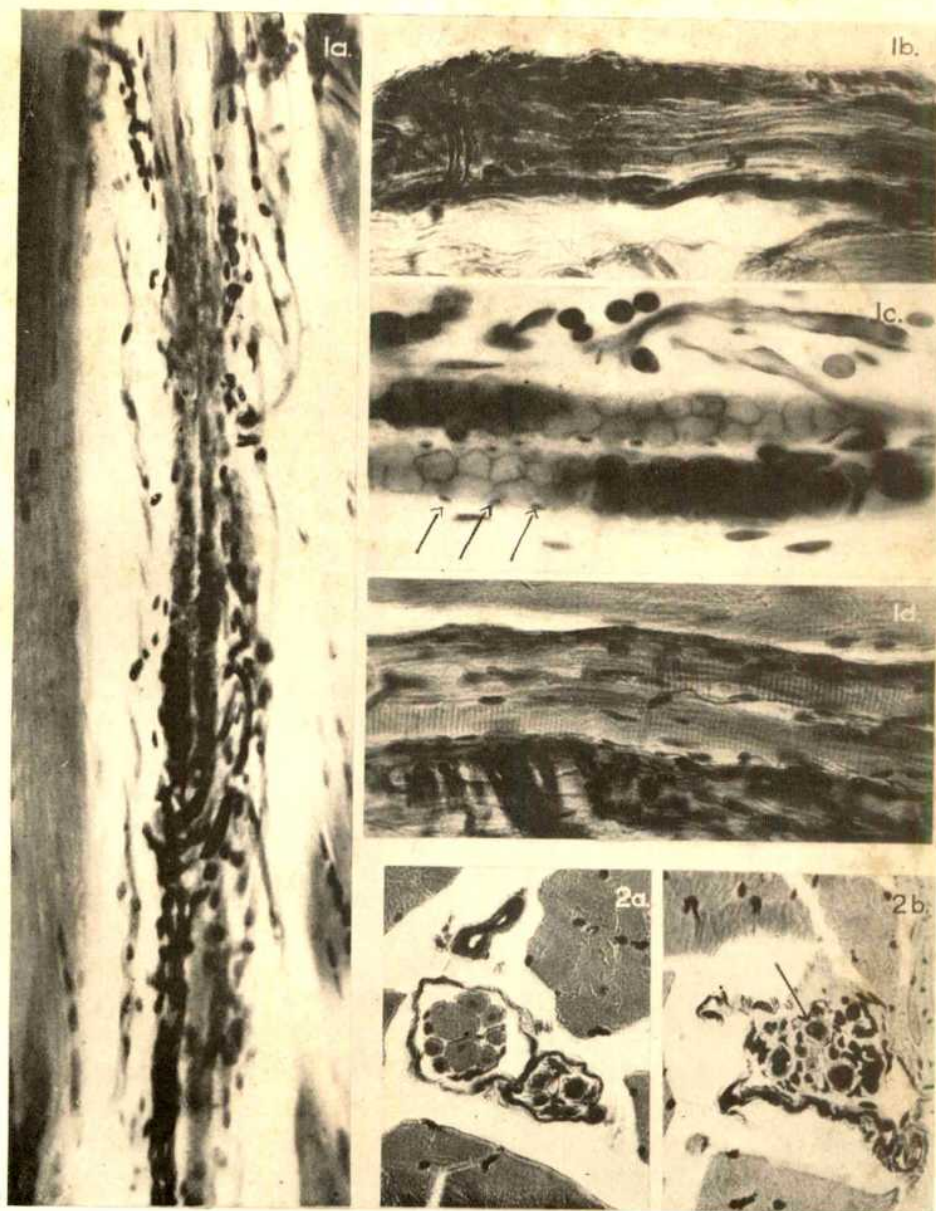
DISCUSSION.

The dorsal and ventral spinal roots share the responsibility for maintaining the muscle spindle in a normal trophic state, as they share its innervation. The sympathetic nervous system, which enters into the spindle probably only in a vasomotor capacity, does not participate in this function. So much is clear. But the manner in which the spinal roots share control is less obvious. The beneficent effect of one intact innervation is not transmitted throughout the cell. Rather, at first glance, it seems to be locally exercised over that portion of the spindle where its nerve endings predominate. From another point of view, however, the atrophy attending root lesions was less spatially distributed than functionally. Those structures of the intrafusal muscle fibre differentiated for a certain function, atrophied when that function fell into disuse through denervation. And subsequently, the portions so affected, degenerated. Thus, after motor-root section, the polar regions showed the greatest atrophy, but it was not so much the polar regions, as the contractile substance, the cross-striated substance, which was

reacting. Even at the equator this material was perceptibly reduced, even degenerated, and only the equatorial aggregate of nuclei, which cannot be conceived of as contractile, was unaffected. Following sensory denervation, on the other hand, this nuclear aggregation was shrunken and dispersed, and the cross-striated substance increased. The contractile structure was, as it were, usurping the entire fibre.

If our surmise is correct, that the annulo-spiral ending is an organ excited by the action currents of the intrafusal muscle fibres, it might be argued that ventral root section would abolish together both the motor and sensory functions of the spindle. However, the spindles occurring in the cat's interosseous muscles are complex sensory organs, although all spindles, those of the frog for example (Hines, 1931), are not. Besides the annulo-spiral ending, which appears to be the organ responding to active contraction and responsible for proprioceptive inhibition, there are other clearly-defined sensory structures. The flower-wreath endings (second order endings of Ruffini) and the knob-like endings resemble organs found in the intramuscular and subcutaneous connective tissue. They suggest structures reacting to passive disturbance. It is possible that these are the afferent organs of the stretch reflex. Moreover, free terminals of finely myelinated or unmyelinated nerve fibres are also present. Even in the failure of active contraction, these latter varieties of sensory ending may still function. And thus their host tissue, the intrafusal fibre, may be preserved from the regressive changes of disuse.

The effect of sensory denervation on the spindle is, however, not so simply explicable. The sensory endings of the spindle are generally considered to be epilemmal; closely applied to the surface of the muscle fibre but not penetrating into its substance. The aggregation and form of the equatorial nuclei suggest a region of extraordinarily high metabolism under the lead-off of the spiral ending. This region is presumably activated through motor nerve endings situated toward the poles, and the sensory nerve endings by it in turn. What sort of influence, then, is exerted, antidromically as it were and across two cell surfaces, by the sensory endings on the muscle? The changes in this region following sensory denervation would seem to be in a class with transneuronal degeneration in the central nervous system. If this is atrophy of disuse, one is led to wonder how the spindle would react to section of the dorsal roots proximal to the ganglion. The loss of function for the animal as a whole would be the same, yet there would be no physical degeneration of nerve tissue contiguous to muscle.



All figures on this and the following plates are untouched photomicrographs. All except figures 1d and 6a are contact prints, and the sizes of objects taken with the same objective and ocular, are comparable. Figures 1a and 6a were enlarged $\times 2$. Apochromatic objectives and compens oculars were used throughout.

Normal spindles in the left fore-leg of cat S IIe.

FIGS. 1a-d.—Spindle from the fifth interosseous muscle. (a) Central region of spindle under low magnification, taken to show the width and thickness of the capsule and intra-fusal muscle bundle. The sensory innervation enters from the left. 8 mm. objective, $\times 7$ ocular. (b) Proximal pole of the same spindle, showing a nerve ending of the motor type. 4 mm. $\times 10$. (c) Detail under oil, of the equatorial region of fig. 1a. The arrows indicate the annulo-spiral nerve ramifications cut across. 2 mm. $\times 10$. (d) Distal pole of the same spindle, showing the coarse striation characteristic of spindle muscle. 4 mm. $\times 10$.

FIGS. 2a and b.—Spindle from the fourth interosseous muscle. (a) Pole, 1 mm. proximal to the maximum equatorial development. 4 mm. $\times 10$. (b) Maximum equatorial development. Arrow indicates a nerve ramification embedded in the cytoplasm of the muscle fibre. 4 mm. $\times 10$.

PLATE IV.



Spindles in the right leg of cat S IIe, killed one year after section of the right brachial plexus.

FIGS. 3a-c.—The most normal appearing spindle remaining in the fifth interosseous muscle. (a) Equatorial region, showing reduction in size of the nuclei, and fibrous degeneration; the latter, especially clear at the lower end. 4 mm. $\times$ 10. (b) Proximal pole, showing vacuolar degeneration in the upper fibre, and fibrosis in the lower. 4 mm. $\times$ 10. (c) Detail of the equatorial region under oil, showing the changes in the nuclei, especially confluence. 2 mm. $\times$ 10.

FIGS. 4a and b.—Spindle from the same muscle showing more advanced degeneration. (a) Equatorial region, showing extreme reduction of the nuclei. 4 mm. $\times$ 10. (b) Proximal pole, muscular tissue completely degenerated; nothing but capillaries and fibrous tissue remaining. 4 mm. $\times$ 19.

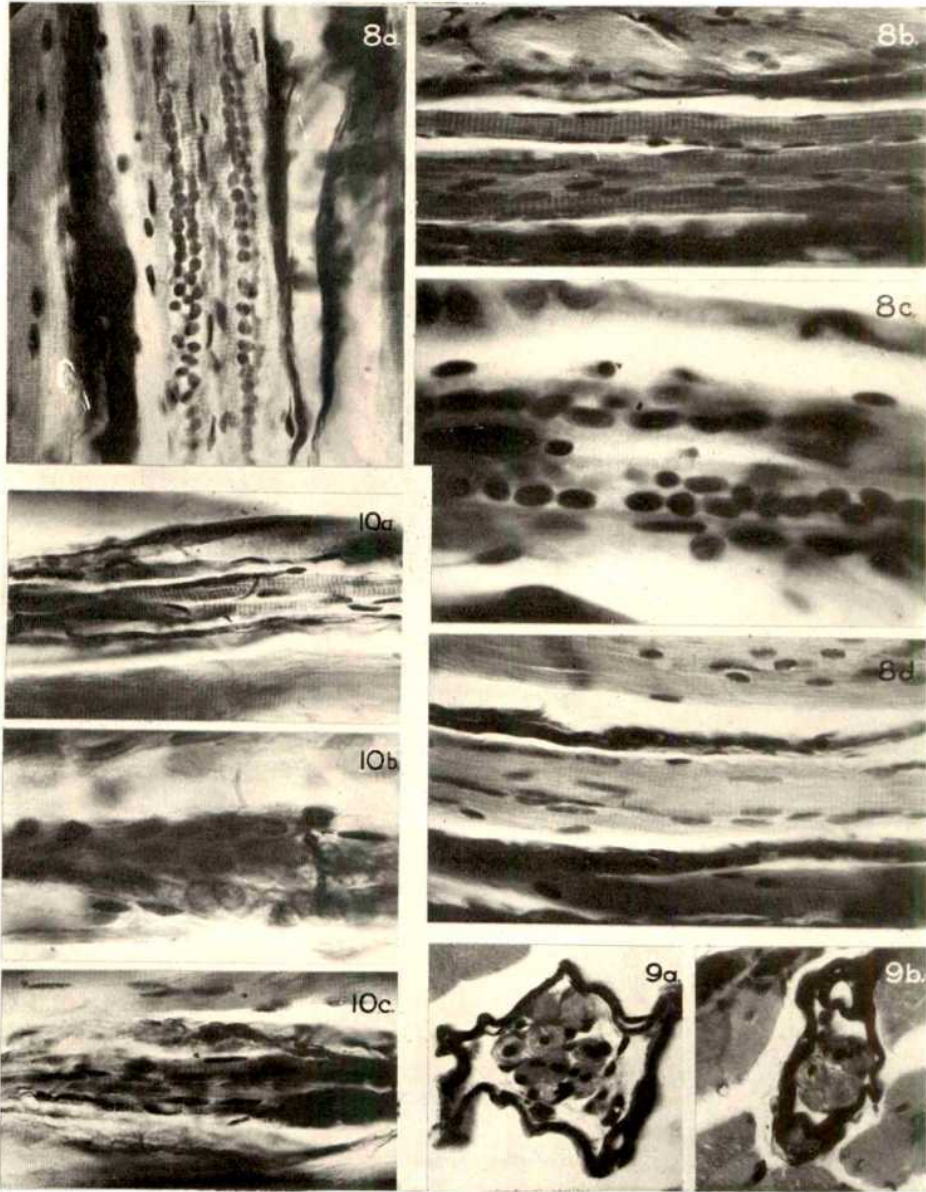
FIGS. 5a and b.—Spindle from fourth interosseous muscle. (a) Pole 1 mm. proximal to maximal equatorial development, fairly well preserved. 4 mm. $\times$ 10. (b) Maximum equatorial development showing, in cross-section, the condition shown in 3c. 4 mm. $\times$ 10.



Spindles from the right fifth interosseus muscle of cat S XIc, killed one year after section of the right ventral roots C_6 to T_2 .

FIGS. 6a-c.—Spindle with intact equatorial innervation but no polar innervation. (a) Central region of spindle under low magnification, taken to show the enormously dilated and thickened capsule, and the sensory nerve fibres. (b) Proximal pole of the spindle, showing advanced degeneration of the muscle fibres, total loss of cross-striation and segmentation. The greatly dilated capillary tuft in the corner is also characteristic. 4 mm. $\times 10$. (c) Detail under oil of the equatorial region, to show the well-preserved nuclei with sharp nucleoli. 2 mm. $\times 10$.

FIG. 7a-c.—Spindle presenting more severe alteration. (a) Proximal pole, showing an extreme degree of vacuolar degeneration in the lower muscle fibre, with a fibrous process in the upper. 4 mm. $\times 10$. (b) Equator, showing general atrophy, but intact nuclei and nucleoli. 4 mm. $\times 10$. (c) Distal pole, showing degeneration. 4 mm. $\times 10$.



FIGS. 8a-d.—Spindle from the right fifth interosseous muscle of cat S VIIId, killed one year after excision of the right dorsal root ganglia C_6 to T_2 . (a) Equatorial region, showing the reduction in number and size and confluence of the nuclei, and the presence of cross-striated muscle substance continuously throughout this region. 11 mm. $\times 10$. (b) Distal pole showing clear-cut cross-striation. 4 mm. $\times 10$. (c) Detail of equator under oil, showing the nuclear changes—shrinkage, elongation and confluence. 2 mm. $\times 10$. (d) Proximal pole. 4 mm. $\times 10$.

FIGS. 9a and b. Same animal, spindle from fourth interosseous muscle. (a) Maximum equatorial development, showing the great quantity of cytoplasm around the much reduced nuclei. Compare with 2b. 4 mm. $\times 10$. (b) Pole 1 mm. distal to maximum equatorial development. 4 mm. $\times 10$.

FIGS. 10a-c. Spindle from the right fifth interosseous muscle of cat S Vc, killed one year after removal of the right stellate ganglion and cervical sympathetic chain. (a) Proximal pole; quite normal. 4 mm. $\times 10$. (b) Detail of equatorial nuclei under oil. 2 mm. $\times 10$. (c) Distal pole, also quite normal. 4 mm. $\times 10$.

Moreover, it may be questioned if the annulo-spiral ending is in reality epilemmal. In the equatorial region the muscle fibre loses the clear-cut contour which is conferred on the polar regions by a well-developed sarcolemma. The subdivision of the fibres at the equator may be an expression of this lack of a containing membrane. Repeatedly, in sections through equatorial regions, the finer ramifications of the annulo-spiral ending appeared to be embedded in the sarcoplasm of the muscle fibre (fig. 2*b*—arrow). Particularly was this true in the angles or chinks between nuclei where there was an accumulation of cytoplasm. In figure 1*c*, such fine ramifications are seen cut across, as fine black dots along the borders of both of the muscle fibres. It is possible, of course, that the embedding of the nerve fibres in the muscle fibre was an artifact of fixation. However, recent studies, in particular those of Heringa (1920), have emphasized the exceedingly intimate relationship of sensory nerve endings, as well as motor, to peripheral non-nervous structures. Should it prove to be true that the annulo-spiral ending is intra-cytoplasmic, then, in the close structural and functional association of the nervous and non-nervous elements in the sensory ending, a subtle metabolic reciprocity may so operate that the peculiar form of one of the tissues is maintained, as perhaps it was originally developed, only in the presence of the other tissue, and the inadequate concept of disuse atrophy need not be invoked.

That such is not also the mechanism of degeneration following motor denervation, remains to be proven. In a previous study (Tower, 1931) the author has pointed out that sensory denervation of the cat's forelimb, which greatly reduces the use of the limb musculature, leads to no appreciable atrophy. Certainly it entails no degeneration. For degeneration a motor lesion is essential. The distribution of the regressive changes in muscle following root lesions may be an exposure, not of the extent of the tissue falling into disuse, but of the actual extent of a syncytial structure of nerve and muscle. A physical representation of this is afforded by the apparent continuity of the neurofibrillæ through the periterminal net with the anisotropic discs of the muscle fibre. Such pictures, as well as the seemingly intracellular position of the annulo-spiral ending, may well be artifacts of fixation in their clarity. But it is scarcely to be doubted that they express a true condition of protoplasmic continuity of nerve and muscle. In disturbance of the metabolic relationships of two tissues so closely interwoven, both physically and functionally, a more convincing basis or the profound disorder following denervation is to be found than in the more simple concept of disuse.

SUMMARY.

In a series of fourteen young adult cats four varieties of lesion were produced: peripheral nerve section, ventral root section, dorsal root, and sympathetic ganglion excision. Four, six or twelve months later, the animals were killed and Bielschowsky silver preparations of muscle made. The muscle spindles of the fifth and fourth interosseous muscle were counted and carefully studied.

Following peripheral nerve lesions the spindle muscle reacted virtually in the same manner and in the same time as did the extrafusal muscle. The fibres shrank; the nuclei swelled; the cross-striation faded; the longitudinal deepened, and the end-product was fibrous tissue. The capsular connective tissues also increased.

With ventral root section the polar portions of the spindle atrophied and degenerated, and the capsule thickened. After removal of the dorsal root ganglia, the reaction was confined to the equatorial region of the muscle fibres. Sympathetic denervation was without effect on the spindle fibres or capsules.

These findings are analysed from the point of view of disuse atrophy, but their possible interpretation on the basis of a metabolic interdependence of nervous and non-nervous tissues is discussed.

BIBLIOGRAPHY.

- BATTEN F. E. *Brain*, 1897, **20**, 138.
 BOEKE, J. *Verhandelingen der Konink. Akad. v. Wetensch. te Amsterdam*, 2^e Sectie, 1916, D, **18**.
 HERRINGA, G. C. *Ibid.*, 2^e Sectie, 1920, D, **21**, 1.
 HINES, M. Unpublished observations, 1931.
 HINES, M. and S. S. TOWER. *Johns Hopkins Hosp. Bull.*, 1928, **42**, 264.
 HINSEY, J. C. *Journ. Comp. Neurol.*, 1927, **44**, 87.
 HOBBSLEY, V. *Brain*, 1897, **20**, 375.
 ONANOFF, I. *C. R. Soc. de Biol.*, 1890, 432.
 RUFFINI, A. *Brain*, 1897, **20**, 368.
 SHERRINGTON, C. S. *Journ. Physiol.*, 1894, **17**, 211.
 TOWER, S. S. *Brain*, 1931, **54**, 97.
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INORGANIC CONSTITUENTS OF THE CEREBROSPINAL FLUID.

III.—MAGNESIUM AND CALCIUM IN MENINGITIS.

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INTRODUCTION.

MORE magnesium is normally present in the cerebrospinal fluid than in the serum or plasma of the blood taken at the same time. Cohen [1], Stary, Kral and Winternitz [12], and McCance and Watchorn [8] have each established this fact independently in more than 120 cases, rather over half of which were reported by McCance and Watchorn. Unlike the cerebrospinal fluid, oedema fluid has always been found to contain *less* magnesium than the corresponding serum (Magnus Levy [7], Salvesen and Linder [11]), and this is also true of the ocular fluids (Duke Elder [3, 4], Tron [14]). Ultrafiltrates have also been found to contain less magnesium than their sera (Tschimber and Tschimber [15], Stary and Winternitz [13], Watchorn and McCance [17]), and the magnesium found in oedema and ocular fluids can be satisfactorily explained on the basis of ultrafiltration. It is certain, however, that the magnesium in the cerebrospinal fluid cannot be so explained.

In addition to finding more magnesium in the cerebrospinal fluid than in the serum, Cohen [1] found that the cerebrospinal fluid magnesium was very constant in amount (average 3.28 mgm. per 100 c.c.), and that an intramuscular injection of a magnesium salt which greatly increased the serum magnesium for a short time did not raise the magnesium in the cerebrospinal fluid. McCance and Watchorn [8] confirmed this relative constancy of the cerebrospinal fluid magnesium (average 3.33 mgm. per 100 c.c.) and found that this was maintained with pathological serum values ranging from 2.0 to 4.05 mgm. per 100 c.c. (normal: 2.35 to 2.65 mgm. per 100 c.c.).

Among his series of eighteen cases, Cohen recorded two cases of

tuberculous meningitis in which the cerebrospinal fluid contained less than the normal amount of magnesium. One contained rather less than the serum (in mgm. per 100 c.c.) and the other almost the same amount. Stary, Kral and Winternitz [12] also recorded two cases of tuberculous meningitis, in which the serum value equalled or slightly exceeded a low cerebrospinal fluid value. They analysed, however, three other fluids in which the magnesium was as low or lower than in the tuberculous ones. And although they found in general that the magnesium in the cerebrospinal fluid bore no relationship to the serum, yet they concluded on the basis of two cases that a serum magnesium greater than the cerebrospinal fluid magnesium was characteristic of tuberculous meningitis.

Eisler [5] found the magnesium in the cerebrospinal fluid constantly raised in meningitis, but all his figures are so low that his results must be accepted with reserve.

The calcium in the cerebrospinal fluid has been very much more studied than the magnesium. The literature has been so well summarized by Critchley and O'Flynn [2] and Walter [16], and to a lesser extent by Stary, Kral and Winternitz [12], that it is unnecessary to do so here. It is still uncertain whether ultrafiltration alone under all conditions can explain the calcium found in the cerebrospinal fluid. Merritt and Bauer [9] have concluded that it can, but Watchorn and McCance [17], who have discussed this point recently, have advanced experimental and other evidence that this simple explanation may not be sufficient to cover all the observed facts.

SOURCE OF MATERIALS AND TECHNIQUE.

Most of the material has been obtained from the general and children's wards of King's College Hospital, but some has been obtained from the Belgrave Hospital for Children and some from St. Giles' Hospital. A few isolated cases have been obtained from other centres. The taking of the blood and cerebrospinal fluid and the analytical technique were fully described by McCance and Watchorn [8], and need not be repeated here. The blood has always been withdrawn before the cerebrospinal fluid, since Cohen has stated that lumbar puncture may raise the serum magnesium. The figures given for chlorides have been taken from the routine King's College Hospital records, or, if the material was obtained elsewhere, determinations were, if possible, specially made by the same method (i.e., direct titration of the cerebrospinal fluid with silver nitrate, using pot. chromate as indicator).

RESULTS.

Table I contains all the experimental results. The diagnosis (column 3) has been accepted (i) if post-mortem confirmation was obtained; (ii) if organisms were seen in direct smears of the cerebrospinal fluid or grown therefrom, and if the clinical findings and course were in agreement. In a number of cases it has not been possible to obtain blood with the cerebrospinal fluid.

DISCUSSION OF THE RESULTS.

Of the 65 cases of general and neurological diseases reported by McCance and Watchorn, only 4 had cerebrospinal fluid magnesium values below 3.00 mgm. per 100 c.c., and only 2 of these were below 2.95 mgm. per 100 c.c. The lowest was 2.83 mgm. per 100 c.c. Of the present series of 33 cases of meningitis covering 46 separate samples of cerebrospinal fluid, only 21 of the latter were over 3.00 mgm. per 100 c.c., and only 6 of these were above the average non-meningitic figure (3.33 mgm. per 100 c.c.). Fifteen were below 2.83 mgm. per 100 c.c. It is quite evident therefore that the cerebrospinal fluid magnesium tends to fall in meningeal inflammation. On making a closer analysis, it is further apparent that:—

(1) None of the *acute* cases, whether meningococcal, *B. friedländer*, pyogenic or pneumococcal in origin, showed a fall. If therefore these are excluded from the general average, practically all the cases of chronic meningitis, whatever the infecting organism, had less magnesium than normal in the cerebrospinal fluid—some of them very much less.

(2) There was a definite tendency for the fall in chlorides and magnesium to run parallel with each other. Thus:—

Chlorides as NaCl— mg. per 100 c.c.		Number of cases		Mg. average mg. per 100 c.c.
Below 640	..	10	..	2.49
640-689	..	18	..	2.95
690 and over	..	9	..	3.81

This relationship is evident, not only statistically but also in most individual cases. Case 27 is an exception. No case with chlorides greater than 700 mgm. per 100 c.c. showed any fall in magnesium.

(3) In the only case (No. 24) which recovered and on whom a series of lumbar punctures was obtained, the magnesium fell during the chronic phase of the disease to rise again to normal during recovery.

(4) The serum magnesium *did not fall* with the cerebrospinal fluid magnesium. The average of the 24 sera was 2.96 mgm. per 100 c.c.

This is well over the upper limits of normal, but agrees very closely with the average of the large series of hospital patients studied by McCance and Watchorn (2.90 mgm. per 100 c.c.). Meningitis therefore appeared to have no specific effect on the *serum* magnesium.

(5) The serum calcium averaged 10.1 mgm. per 100 c.c. and the corresponding cerebrospinal fluids 5.84 mgm. per 100 c.c. These figures may be compared with 10.7 and 5.8 mgm. per 100 c.c., respectively, taken from McCance and Watchorn's series of other non-meningitic diseases. The meningitic $\frac{\text{C.S.F.}}{\text{serum}}$ ratio was 0.577 and the non-meningitic 0.543. These differences are scarcely significant, but they tend to show that relative to the serum there was slightly more calcium in the cerebrospinal fluid in meningitis. Merritt and Bauer [9] found much greater differences between meningitic and non-meningitic cases, and their explanation that the increase of calcium in the meningitic fluids was due to increased capillary permeability may be the correct one. Even in Merritt and Bauer's series, however, all the individual cases did not conform, and there is probably another factor to be considered besides the increased permeability of the choroid plexus to proteins [17].

GENERAL DISCUSSION.

(1) *Practical significance and diagnostic value.*—It is evident in this series of cases that a fall in the cerebrospinal fluid magnesium has been the rule in chronic meningitis. A knowledge of the amount of magnesium in the cerebrospinal fluid therefore in any given case should be a test of diagnostic value; how valuable, only an extended trial can determine. Meanwhile it is only possible to suggest that (i) a fall in the cerebrospinal fluid magnesium is not peculiar to any one type of meningitis; (ii) so far a fall has never been observed in an acute case; (iii) the return to normal or towards normal may be of prognostic significance (Case No. 24); (iv) at present a fall in magnesium appears to have somewhat the same significance as a fall in chlorides, and as the determination of chlorides is much easier than that of magnesium, no one would willingly replace the former by the latter if only one chemical test were to be made.

(2) *Theoretical significance.*—On four carefully studied cases, Linder and Carmichael [6] have shown that the fall in chlorides in the cerebrospinal fluid is accompanied by a fall in the plasma chlorides, so that the normal $\frac{\text{C.S.F.}}{\text{serum}}$ ratio remains unchanged. There appears at

present no prospect of explaining the fall in magnesium on similar simple lines. It is in fact very difficult on physico-chemical grounds to explain why the fall in an anion (Cl) should be accompanied by a fall in a kation (Mg) which relative to the Cl ion is present in insignificant amounts. The parallelism may be entirely fortuitous. It is unwise at present to attempt to explain any movements in cerebrospinal fluid magnesium in the light of an alteration of permeability affecting a "Donnan" membrane equilibrium (1), for the magnesium normally found in the cerebrospinal fluid cannot be so explained. Stary, Kral and Winternitz [12] have suggested that the magnesium in the cerebrospinal fluid is normally above the serum because the extra magnesium diffuses in from the surrounding brain matter. This is not a satisfactory explanation because: (i) When the serum rises very high the cerebrospinal fluid does not follow, but tends to remain constant. One would not expect this if the cerebrospinal fluid magnesium were made up of the sum of the ultrafiltrable serum magnesium and the magnesium leaking in from the brain tissue. (ii) It is difficult to understand why in meningitis less magnesium should diffuse into the cerebrospinal fluid than before.

Collecting together all the evidence of Cohen [1], Stary, Kral and Winternitz [12], McCance and Watchorn [8], and Watchorn and McCance [17], it is difficult to escape from the conclusion that the magnesium in the cerebrospinal fluid is normally fixed at a definite level by some active cellular process. This is not in any way antagonistic to the view that the *total* concentration of electrolytes in the cerebrospinal fluid is governed by a process of physical diffusion [10], for compensatory changes will take place in the freely diffusible ions so that thermodynamical equilibrium with the plasma is attained. On the above basis the meningitic changes may be explained either: (1) As a partial loss by the active cells of their power to fix the cerebrospinal fluid magnesium at a constant level. Local toxæmia might cause this loss. The cerebrospinal magnesium would then tend to take up its ultrafiltration level, and would show a fall unless the serum magnesium were very high indeed [17]. (2) As an alteration in the level at which the cellular process stabilizes the fluid magnesium. This seems the more probable of the two. Case No. 1, with serum magnesium 3.81 mgm per 100 c.c. and fluid magnesium 2.90 mgm. per 100 c.c., gave from the serum an ultrafiltrate containing 3.38 mgm. per 100 c.c. This is outside the experimental error of the method [17] and shows that in this case, at any rate, the fluid magnesium was being maintained *below* the ultrafiltration level.

TABLE I.

No.	Age	Diagnosis	MAGNESIUM		CHLORIDES	CALCIUM		Remarks
			Serum mg. per 100 c.c.	C.S.F. mg. per 100 c.c.		Serum mg. per 100 c.c.	C.S.F. mg. per 100 c.c.	
1	6	Tuberculous meningitis	3.81	2.90	660	12.08	5.68	—
2	22	"	3.51	3.87	692	10.85	6.38	Very early case
3	11	"	3.17	2.61	600	9.51	5.59	—
4	—	"	3.2	2.35	610	9.61	5.20	—
5	18	"	3.89	2.98	610	10.68	5.59	—
6	11	"	2.61	2.88	—	11.06	4.84	—
7	12	"	3.64	3.11	666	12.50	7.90	—
8	11	"	2.86	2.44	620	9.70	6.10	—
9	7	"	2.94	2.74	652	9.31	4.16	—
10	6	"	2.97	2.91	665	8.81	5.35	Material collected 15.6.31
			—	2.91	672	—	5.94	" " 16.6.31
11	26	"	2.75	2.37	595	9.90	5.10	" " 27.6.31
			2.42	2.21	575	9.50	6.00	" " 28.6.31
			2.88	2.47	620	9.80	—	" " 30.6.31
12	5	"	3.01	3.06	680	10.39	5.78	Diagnosis not proved. No p.m.
13	36	"	3.33	2.68	680	9.11	6.37	Material collected 16.10.31
			3.31	2.94	640	8.72	6.57	" " 20.10.31
14	20	"	3.14	2.60	610	10.09	6.86	—
15	16	"	2.67	3.11	700	10.29	5.59	Material collected 20.10.31
			2.59	2.85	690	9.11	5.39	" " 3.11.31
16	—	"	—	2.88	650	—	7.98	—
17	7	"	—	3.11	640	—	4.02	—
18	3	"	—	2.66	640	—	4.85	—
19	38	"	—	2.78	670	—	6.90	—
20	13	"	—	3.21	690	—	5.98	Diagnosis not proved. No p.m.
21	2	"	—	3.08	640	—	5.39	Material collected 7.9.31
			—	3.08	—	—	5.29	" " 8.9.31
			—	3.08	—	—	—	" " 10.9.31
22	1	Pneumococcal meningitis	3.16	2.54	620	12.08	7.62	Chronic case. Material collected 1.6.31
			—	2.58	680	—	7.08	Material collected 6.6.31
			—	2.46	620	—	5.84	" " 12.6.31
23	—	"	—	3.47	—	—	4.61	Acute case
24	4	"	—	3.42	690	—	6.58	Chronic course. Material collected 5.6.31
			—	3.19	—	—	5.69	Material taken 6.6.31
			—	2.82	—	—	5.54	" " 10.6.31
			—	3.42	670	—	4.95	Recovering. Material taken 13.6.31
25	5	"	—	3.11	709	—	5.30	—
			—	3.14	—	—	5.60	—
26	—	"	—	3.00	—	—	5.59	—
27	12	Streptococcal meningitis	3.62	3.68	640	10.09	5.10	—
28	—	<i>B. friedländer</i> meningitis	—	3.33	—	—	4.85	—
29	—	Probably pyogenic	—	3.32	770	—	7.23	Diagnosis uncertain. Acute onset. No p.m.
30	8	Pyogenic meningitis	2.52	3.33	722	10.10	—	Following bilateral mastoid infection
31	—	"	4.64*	2.91	665	10.69	5.15	Chronic course; secondary to infected mastoid
32	13	Meningococcal meningitis	3.19	3.59	760	10.39	7.35	—
33	12	"	3.28	3.32	756	8.72	5.29	Quoted from McCance and Watchorn, <i>Quart. Journ. Med.</i> , 1931, 24, 371

* Serum slightly hemolysed, omitted from averages.

SUMMARY.

(1) In chronic meningitis (tuberculous or pneumococcal) subnormal amounts of magnesium have been found in the cerebrospinal fluid. A fall has not been observed in the acute cases.

(2) The fall in the magnesium in meningitis has been found roughly to run parallel with the well-known fall in chlorides.

(3) In one case which recovered the cerebrospinal fluid magnesium returned to normal.

(4) The determination of cerebrospinal fluid magnesium should be of diagnostic value.

(5) The cerebrospinal fluid calcium showed little, if any, significant change in meningitis.

(6) The theoretical significance of these results has been discussed.

We wish to express our thanks to all those who have in any way helped us to obtain material for this work.

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REFERENCES.

- [1] COHEN, H. *Quart. Journ. Med.*, 1926-27, **20**, 173.
- [2] CRITCHLEY, M., and O'FLYNN, E. *Bram*, 1924, **47**, 337.
- [3] DUKE-ELDER, W. S. *Biochem. Journ.*, 1927, **21**, 66.
- [4] *Idem.* *Brit. Journ. Ophthalmol.*, 1927. Monograph Supp. iii.
- [5] EISLER, B. *Zeitschr. f. ges. exp. Med.*, 1928, **61**, 549.
- [6] LINDER, G. O., and CARMICHAEL, E. A. *Biochem. Journ.*, 1928, **22**, 46.
- [7] MAGNUS LEVY, A. *Zeitschr. klin. Med.*, 1919, **88**, 1.
- [8] MCCANCE, R. A., and WATCHORN, E. *Quart. Journ. Med.*, 1931, **24**, 371.
- [9] MERRITT, H. H., and BAUER, W. *Journ. Biol. Chem.*, 1931, **90**, 215, 283.
- [10] PINCUS, J. B., and KRAMER, B. *Ibid.*, 1933, **57**, 463.
- [11] SALVESEN, H. A., and LINDER, G. O. *Ibid.*, 1928-24, **58**, 617.
- [12] STARY, Z., KRAL, A., and WINTERNITZ, R. *Zeitschr. f. ges. exp. Med.*, 1929, **66**, 671.
- [13] STARY, Z., and WINTERNITZ, R. *Zeitschr. f. physiol. Chem.*, 1929, **182**, 107.
- [14] TRON, E. *Arch. f. Ophthalmol.*, 1927, **118**, 718.
- [15] TSCHIMMER, H., and TSCHIMMER, O. *Compt. Rend. Soc. Biol.*, 1924, **91**, 592.
- [16] WALTER, F. K. "Die Blutliquorschranke." Leipzig. 1929.
- [17] WATCHORN, E., and MCCANCE, R. A. *Biochem. Journ.*, 1932, **26**, No. 1. In Press.

TONIC PUPILS AND ABSENT TENDON REFLEXES: A BENIGN DISORDER *SUI GENERIS*; ITS COMPLETE AND INCOMPLETE FORMS.

BY W. J. ADIE.

THE tonic pupillary reaction (syn. pupillotonia, myotonic convergence reaction, tonic convergence reaction of pupils apparently inactive to light) has been known to ophthalmologists since 1902 when Saenger and Strasburger described it independently.

Last year, under the title "Pseudo-Argyll Robertson pupils with absent tendon reflexes: a benign disorder simulating tabes dorsalis," I gave an account of five cases in which I found typical tonic pupillary reactions associated with loss of some or all of the deep reflexes in the upper and lower limbs. In the meantime I have seen eight more of these cases. I have found, too, mainly in journals devoted to ophthalmology, reports of forty-four cases presenting the tonic pupillary reaction; in nine of these absence of reflexes is recorded.

I use these twenty-two cases to establish the existence of the disorder I am about to describe in what I call its complete form. It is characterized by the presence of the tonic pupillary reaction in its most characteristic form and absence of one or more of the tendon reflexes.

Since 1878 when Jonathan Hutchinson introduced the term *ophthalmoplegia interna* many papers have appeared on this subject giving series of cases with analyses according to the supposed cause. In every series there is a large group in which the cause of the eye signs was unknown; twelve of Uhthoff's thirty cases are included under this heading. I suggest that most of these cases of "*ophthalmoplegia interna unilaterale*" in otherwise healthy young patients are examples of the disorder that concerns us here. I base this synthesis on my interpretation of the pupillary signs. According to this interpretation the "*iridoplegia*" or "*ophthalmoplegia interna*" in these cases represents a phase of the tonic pupil that may either precede the appearance of typical tonic reactions, or appear as an exacerbation in a pupil that had previously presented tonic reactions. Cases of this kind will be referred to as incomplete forms of the disorder.

Author	Year	Sex	Age	Reflexes	Blood and c.s.f.	Author's remarks	
Nonne ..	1902	M.	40	A. Jerks absent R. and L.	—	No evidence of syphilis. Loss of ankle-jerks due to diabetes	
Marcus ..	1906	M.	12	K.J. absent R. and L.	—	The signs "might be considered sufficient evidence of congenital syphilis. I am, however, inclined to take a less serious view"	
Oloff ..	1	1914	M.	18	K.J. absent R. and L.	Blood negative; c.s.f. normal	No comment
	2	1914	M.	44	K.J. absent R. and L.	—	As yet no other signs of tabes or G.P.I.
Jess ..	1914	M.	21	Right A.J. absent	Blood negative	No comment	
Lerperger ..	1914	M.	32	No details ..	—	Neurological examination suggests incipient tabes	
Axenfeld ..	1919	F.	19	Triceps, K.J. and A.J. absent R. and L.	Blood once suspicious, once negative	Probably congenital lues	
Gehroke ..	1921	F.	45	A.J. absent R. and L.	Blood negative; c.s.f. normal	Seems to be a case of imperfect stationary tabes	
Behr ..	1921	F.	55	A.J. absent R. and L.	Blood negative; c.s.f. normal	Organic nervous disease may be excluded	
Weill and Reys	1926	M.	26	K.J. feeble, A.J. absent R. and L.	Blood negative; c.s.f. normal	Signs attributable to polyneuritis after rheumatic fever or influenza	
Foster Moore	1	1931	F.	49	K.J. absent, R. and L.	—	Not in any way related to syphilis
	2	1931	F.	16	K.J. very sluggish, R. greater than L.	—	—
Adie ..	1	1931	F.	36	All reflexes absent	Blood negative; c.s.f. normal	A benign disorder <i>sui generis</i> ; no relation to syphilis
	2		F.	28	K.J. and A.J. absent R. and L.	Blood negative; c.s.f. normal	—
	3		M.	82	All absent ..	Blood negative; c.s.f. normal	—
	4		F.	17	K.J. brisk R. and L.; A.J. very sluggish R. and L.	Blood negative; c.s.f. normal	—
	5		F.	45	A.J. absent R. and L.	Blood negative; c.s.f. not examined	—
New cases—	6		F.	48	K.J. and A.J. absent R. and L.	Blood negative; c.s.f. normal	—
	7		F.	24	K.J. brisk R., absent L.; A.J. sluggish R., absent L.	Blood negative; c.s.f. normal	—
	8		F.	35	K.J. and A.J. absent R. and L.	Blood negative; c.s.f. normal	—
	9		F.	18	All absent ..	Blood negative; c.s.f. normal	—
	10		F.	60	K.J. and A.J. absent	Blood negative	—
	11		F.	81	K.J. brisk R., absent L.; A.J. absent R., sluggish L.	Blood negative	—
	12		F.	17	A.J. absent R. and L.	Blood negative	—
	13		F.	23	A.J. absent R. and L.	—	—

Every experienced neurologist has seen a few patients with absence of the tendon reflexes for which no cause could be found. Acting on the suggestion of Dr. James Collier, I mention these cases here and submit that some of them are incomplete examples of this disorder. For proof I await a case in which a tonic pupil appears under observation.

If my views are correct the disorder I am describing may manifest itself in the following forms:—

- (1) The complete form—typical tonic pupil and absence of reflexes.
- (2) Incomplete forms: (a) tonic pupil alone; (b) atypical phases of the tonic pupil alone (“iridoplegia”; “internal ophthalmoplegia”); (c) atypical phases of the tonic pupil with absent reflexes; (d) absent reflexes alone.

THE TONIC PUPIL.

In its most characteristic form the tonic pupil is usually unilateral and almost always larger than its normal fellow; it is never miotic.

When the usual bedside methods are used the reaction to light, direct and consensual, appears to be completely or almost completely absent; after a sojourn in a dark room for an hour or so the pupils dilate to an equal size; thereafter, on exposure to bright diffuse daylight, the abnormal pupil, perhaps after a short delay, contracts slowly; this contraction may continue until the pupil becomes smaller than it was before it dilated in the dark; it then, again after a short delay, dilates to its original size. The most important feature of the tonic pupil is its behaviour on convergence. If the patient fixes a near object and continues to gaze at it intently the pupil, sometimes after a delay of several seconds, contracts slowly and with increasing slowness through a range often greatly in excess of the normal; contraction down to pinhead size is not uncommon; the larger abnormal pupil then becomes smaller than its fellow. After the effort to converge is relaxed the pupil continues to contract, or remains fixed for a few seconds, or begins to dilate slowly again at once; dilatation once begun proceeds at a slower rate than contraction, so that many seconds or several minutes may elapse before it reaches its original size. Accommodation may be affected in the same manner; the defect is noticed most often during relaxation; after fixation of a near object some seconds elapse before distant objects become clear. There is no constant relation between the rate of contraction of the iris on convergence and of the ciliary muscle during accommodation in the same case (Axenfeld).

The same slow dilatation can sometimes be observed after the pupil has contracted on forcible closure of the lids (tonic lid-closing reaction).

The tonic pupil dilates fully and promptly to mydriatics and contracts under eserine.

In nineteen cases that I have examined myself, the abnormal signs were unilateral in fourteen.

There are very few exceptions to the rule that the abnormal pupil is the larger one. I have seen one example and I know of two others (Oloff, Domarus). It may be regularly or irregularly oval with its long axis vertical or horizontal. The pupil often varies in size through a considerable range during the day; it is often at its smallest in the morning; two patients said that a pupil, usually widely dilated, became quite small after they had been crying (probably a tonic lid-closing reaction). Behr states that he saw "ausgesprochener Hippus" confined to the abnormal pupil in three of his cases. In one of Oloff's cases the signs were found now in one eye, now in the other; the abnormal pupil was always the larger one. This is an unique observation. The findings, however, often vary considerably in the same eye at different examinations.

In most of my cases I have been able to confirm the observations that the pupil dilates in the dark (Dimmer), and then contracts in diffuse daylight (Lerperger), sometimes to a size smaller than it was before (Behr). In some of them, however, I obtained no response. In two of my cases with bilateral tonic convergence reactions the response differed in the two eyes on exposing them to light after an hour in the dark room. In one case one pupil contracted slowly and remained small; in another, one pupil contracted, but in this case the response was prompt and not maintained. In both instances the pupil that reacted to light was usually smaller than its fellow and it had varied in size from time to time.

Relaxation after convergence always proceeds much more slowly than the tonic contraction. In a large majority of the cases the pupil remains small for several or many seconds before it begins to dilate again. Contraction and relaxation are slowest, always I think, towards the end of the movement. I know of only one exception to the rule that both movements are always affected. In one of Marcus's patients, contraction on convergence was normal, but dilatation was very slow.

Some of these patients have difficulty in sustaining the act of convergence. If they are not encouraged to persist the presence of the tonic contraction may easily be missed. Repetition does not facilitate movement as it often does in myotonic muscles.

Tonic accommodation is mentioned in but a small proportion of the cases. It has never been observed as an isolated sign.

The foregoing paragraphs deal mainly with the typical tonic pupil in which all movements, though tardy, are normal or excessive in range.

I must now deal with cases that are, according to my view, certainly examples of the same disorder, but have been reported without any reference to the tonic pupillary reaction.

Under the title "Non-luetic Argyll Robertson pupil," Foster Moore has reported fifteen cases characterized by "the complete or substantially complete inaction of the pupil to the light stimulus, the leisurely manner in which it contracts with convergence and in which it again dilates after relaxation of convergence; the frequency with which it is unilateral; the integrity of accommodation; the absence of syphilis; the presence of knee-jerks and the absence of signs of any nervous disease even after many years." His clear description of the pupillary phenomena leaves no room for doubt that he was observing what I call here the tonic pupillary reaction. In most of his cases the condition was discovered in the course of a routine examination; accommodation was defective in one case only. In most of them the knee-jerks were present, in one they were lost; in another they were obtained on reinforcement only. It may be that the arm and ankle jerks were not tested in every case.

Mr. Foster Moore made it possible for me to see several of his patients and he kindly allowed me to read the notes of his unpublished cases. Without any hesitation I conclude that some of them are complete and the remainder incomplete examples of the disorder I have described.

Somewhat more aberrant are the cases in which the abnormal pupillary signs were designated by the terms iridoplegia, internal ophthalmoplegia or fixed pupil.

In the cases of "ophthalmoplegia with absent tendon reflexes," described by Morgan and Symonds, the pupils were said to be either fixed or very sluggish to light and on convergence.

These authors refer to the cases described by Foster Moore, and state that theirs differ from his in several ways. I consider that the differences are of no importance. The fact that accommodation was defective in most of the cases in one group and in only one in the other is fortuitous. The state of the pupil is described differently by the different observers, but I attach much more importance to the points of similarity in the two groups: the presence of abnormal pupillary signs,

mainly unilateral, in healthy young females free from syphilis, some in one group, almost all in the other, also presenting defects in the tendon reflexes.

I feel sure that if the patients described by Foster Moore and by Morgan and Symonds were re-examined it would be found in the first group, where the tonic pupillary reactions were detected, that many of the patients also have loss of reflexes, and in the other group where the reflexes were always affected, that the abnormal pupils already present tonic reactions or that these will be found later if the patients are examined at intervals.

The more carefully I examine these cases the more I am convinced that true iridoplegia is rare. I have a patient in hospital at present whose pupils appear to be fixed to light and on convergence. The patient herself has noticed that they vary in size; sometimes they are quite small. Prolonged exposure to bright diffuse light brings about a definite contraction. The findings on convergence are very instructive: for five seconds or more no movement occurs; then contraction begins and goes on slowly through a wide range; dilatation is still more tardy. On one occasion I counted ten slowly before the contraction on convergence was noticeable.

Nevertheless the pupil in this disorder may be so stiff that at the time of examination no reaction to light or on convergence is obtainable.

Axenfeld, an experienced ophthalmologist with special knowledge of the tonic pupil, saw a young woman at the age of 19 who stated that she had always had unequal pupils; both pupils were then "completely fixed." He examined her again a year later when "a slight contraction occurred on prolonged convergence." Three years later her vision suddenly became defective; at this examination the pupils showed a typical tonic convergence reaction. Accommodation was very slow; after the patient had fixed a near object for thirty seconds, forty seconds elapsed before complete relaxation occurred. The findings were much the same after six and nine years. The knee-jerks and ankle-jerks were absent; the Wassermann reaction in the blood was suspicious on one occasion, negative on another. The signs were attributed, on this evidence, to congenital syphilis.

Reitsch found at a first examination "ophthalmoplegia interna"; four years later the dilated pupil contracted on convergence down to 1.5 mm. in 8 sec. and dilated still more slowly.

One of my patients presented a perfect tonic convergence reaction in

one pupil; in the other, which had recently dilated suddenly, I was unable to obtain any contraction on convergence.

In another, with no history of sudden dilatation, but, like the one just mentioned, with difficulty in accommodating, one pupil was tonic on convergence while the other larger one seemed to be fixed. It may be that my examination was not persistent enough in these cases. Nevertheless they show that in cases certainly belonging to our group the pupils may appear to be inactive on convergence. The cases of Axenfeld and Reitsch tend to confirm the surmise I made in my earlier paper on this subject that the dilated and apparently fixed pupil becomes tonic in the course of time.

The typical tonic pupil then appears to be inactive to light but reacts after a sojourn in a dark room; it contracts slowly on convergence through a wide range and dilates still more slowly. But we must be prepared to encounter many cases of the disorder in which the pupils do not conform strictly to this description. The pupil may contract feebly to light when ordinary methods are used. The reaction to light is often unobtainable by any method; or it may be found in one eye but not in the other when suitable tests are made. The contraction of the pupil may be normal on convergence, dilatation only being delayed. The tonic convergence reaction may be present in one eye while the other pupil is fixed. In unilateral cases the abnormal pupil may be fixed to light and on convergence. The pupil may be fixed at the time the patient is first seen and show tonic reactions later; or a pupil known to be tonic may suddenly dilate and become fixed. Whether such a pupil ultimately becomes tonic again I do not know, but I suspect that it does.

THE RELATION OF THE TONIC REACTION TO OTHER ABNORMAL PUPILLARY REACTIONS.

In so far as the tonic pupil is or seems to be inactive to light but contracts on convergence it conforms to the prevailing loose definition of the Argyll Robertson pupil. It is for this reason that patients with tonic pupils with and without loss of tendon reflexes are almost invariably thought to be suffering from syphilis of the nervous system.

The true Argyll Robertson pupil, as I have emphasized elsewhere, is an infallible sign of syphilis; its characters, as described by its discoverer, are that it is small, usually bilateral, constant in size, and unaltered by light or shade; it contracts promptly and fully on convergence and dilates again promptly when the effort to converge is relaxed; it dilates

slowly and imperfectly to mydriatics. It thus differs from the tonic pupil in every essential particular and can hardly be confused with it by anyone who is familiar with the characteristic features of both anomalies.

Behr's view is that the tonic reaction differs essentially from the other well-known abnormal reactions: Argyll Robertson pupils, fixed pupils and ophthalmoplegia interna.

The tonic reaction was confined to one side in 80 per cent. of the cases I have seen or analysed; the Argyll Robertson pupil, in my experience, is unilateral in about 5 per cent.; the fixed pupil in less than 10 per cent., and ophthalmoplegia interna in about 20 per cent.

The tonic pupil is almost without exception larger than its normal fellow; the unilateral Argyll Robertson pupil is always the smaller.

If we distinguish between small (under 3 mm.) and large pupils the tonic pupil is never small, whereas the Argyll Robertson pupil is small in 75 per cent., the fixed pupil in 9 per cent., and the pupil of internal ophthalmoplegia in 10 per cent. (Behr).

The tonic pupil varies in size from time to time and may show hippus confined to the affected pupil. It often dilates in the dark and then becomes equal in size with its fellow. This never happens to the Argyll Robertson pupil.

The behaviour of the tonic pupil on subsequent exposure to bright diffuse light is peculiar to it. In other abnormal pupils a slight change may be detected in similar circumstances, but the range of the movement is very narrow and contrasts strongly with the full or even excessive movements of tonic pupils.

The tonic reaction on convergence differs from the contraction on convergence of the Argyll Robertson pupil in that in the latter it is typically prompt and dilatation after the act ceases is also prompt.

The fact that the tonic pupil contracts through a normal or wide range suggests that there is no true paralysis or paresis, but some qualitative change in its mobility. This also applies to accommodation: the movement is slow but not reduced in range; it always corresponds to the age of the patient (Axenfeld). This is essentially different from the findings in ophthalmoplegia interna where the narrow range of movement on accommodation is decisive for diagnosis.

Syphilis is an important factor in the production of other abnormalities of the pupil. Here it plays no part.

This evidence supports Behr's contention that the tonic reaction is distinct from all the other known forms and that it is a manifestation

of a disorder *sui generis*. The fact that the extra-ocular nervous phenomena are unlike anything with which we are familiar also supports the view that we are confronted here by a hitherto unknown kind of perversion of nervous activity.

THE TENDON REFLEXES.

In the published reports on forty-four patients with tonic pupils, loss of one or more of the tendon reflexes is mentioned in nine; this is either passed over without comment or accepted as further evidence of the presence of syphilis of the nervous system.

All of these cases were described by ophthalmologists; it is almost certain therefore that the proportion with some defect in the reflexes is much higher than these figures indicate. Of nineteen patients with a tonic pupil that I have seen myself thirteen had abnormal reflexes.

Loss of one or both ankle-jerks is most frequent; I have never seen loss of any other jerks with both ankle-jerks still present. Sometimes one or more of the arm-jerks cannot be obtained at a time when the knee-jerks though sluggish can still be obtained on reinforcement.

Asymmetry is not uncommon. I have seen two cases with the knee and ankle jerks absent on one side and still present on the other. In one of these patients the remaining knee-jerk seemed to be abnormally brisk.

In one of Behr's cases the knee and ankle jerks were absent; three years later the ankle-jerks could be obtained on reinforcement. One of Axenfeld's patients was examined "repeatedly" over a period of nine years by expert neurologists; the triceps, knee, and ankle jerks were absent throughout. I suspect that jerks once lost do not return.

One of Oloff's patients had been in hospital five years before when the knee-jerks were present. At the second examination they were absent. The absence of reflexes therefore is probably not congenital.

GENERAL FEATURES.

Of my own cases fifteen were females, four males. Including the cases described by others, the figures are forty-five females and eighteen males. The proportion of males thus rises when cases with pupillary abnormalities alone are taken into account. It may be that females are not only more susceptible but also that they are more likely to lose their tendon-jerks.

The age at which the signs appear has not yet been determined. Some patients state that the pupils have "always" been unequal.

This was noticed in one of Foster Moore's patients at the sixth month; at the age of 5 years this patient presented typical tonic reactions.

Most of those who complain of sudden mistiness of vision and dilatation of the pupil are in the twenties and thirties; but this gives no indication of the age at which their pupils became tonic, because, as we have seen, a pupil known to be tonic may dilate suddenly at any time and cause visual symptoms.

Mackay examined Bramwell's case, a healthy unmarried woman, in 1894, and found normal pupils; in 1906 when she was about 38 years of age he found unequal pupils with "no apparent reaction to light in either." This is the only case I have been able to find where an expert has found normal pupils at one examination and tonic reactions at another, and this is not a proven case of our disorder.

My impression is that the abnormal pupillary reaction may appear at any age. The cases of Oloff and Axenfeld, already mentioned, suggest that this is true for loss of reflexes also.

In many cases, perhaps in a large majority the disorder is symptomless throughout life. In a few the onset appears to be sudden; in the course of a game perhaps, some discomfort is felt in and around the eye and vision becomes misty; when the eye is inspected it is found that one pupil is dilated and examination reveals defects in accommodation and in its reactions.

I have never heard of a case with symptoms that could be associated with the loss of reflexes in the lower limb. Repeated careful examinations by myself and by my assistants have failed to reveal any other evidence of disturbance of the functions of the muscles or nervous system in patients with absent reflexes.

There is nothing in the family history of these patients to indicate that they belong to a neuropathic or degenerate stock; nor does anything in the personal history recur with sufficient frequency to deserve mention as a possible ætiological factor. Their general health is remarkably good. They are not nervous; they do not conform to any special physical type.

RELATION OF THE DISORDER TO SYPHILIS.

In 1921, when Behr discussed this subject, he had to contend with the fact that most of the writers who preceded him had attributed the tonic pupillary reaction to the effects of syphilis; they based this diagnosis on the ocular signs alone, believing that the tonic pupil was a form of the Argyll Robertson pupil and they made it with still greater

confidence when absence of tendon reflexes seemed to confirm it. Nevertheless, from his study of twenty-one cases in the literature and eight cases of his own, Behr formulated the following cautious conclusion: the presence of pupillotonia alone does not justify the assumption that the patient is suffering from syphilis of the nervous system. Our position now, based on a study of over sixty cases, is much stronger.

The majority of the patients are healthy young females; the ocular signs they present are not observed in syphilitics; in many of them tendon areflexia persists for many years without the addition of any other sign or symptom referable to disease of the nervous system. A patient with evidence that this disorder was present in childhood has lived to the age of 75 without nervous troubles (Foster Moore).

I know of eighteen cases of tonic pupil with absent tendon reflexes in which the blood and cerebrospinal fluid were examined; the results were negative in all. In five more the blood alone was tested, with negative results.

Without making another search throughout all the published reports I cannot give the exact number of the cases of tonic pupil alone in which the blood and cerebrospinal fluid were examined, or the blood only, but tests were made in many cases with negative results in all but one (Barkan's case) in which the reaction in the blood was positive. In this case there was no other evidence of syphilis of the nervous system.

I think the following conclusions may now be drawn with safety: the tonic convergence reaction in pupils only apparently inactive to light is, in all probability, never a manifestation of syphilis of the nervous system. The combination of this sign with absent tendon reflexes and without other signs of organic nervous disease has never been observed in syphilis of the nervous system; it is not one of its manifestations.

DIAGNOSIS.

The diagnosis of this disorder in its complete form presents no difficulty; the combination of the tonic convergence reaction in a pupil apparently inactive to light, with absence of one or more of the tendon-jerks, is pathognomonic.

In the incomplete forms, that is where tonic pupils alone, or "iridoplegia" or "internal ophthalmoplegia," alone or with absent jerks, are found there may be some difficulty.

It must be understood that slowness of movement by itself does not constitute a tonic reaction; that is seen in retinal disease, in traumatic iridoplegia and in many other dissimilar affections of the visual and oculomotor mechanism. The decisive diagnostic features of the true tonic pupil are delay as well as slowness in responding, the inactivity to light which is only apparent, its tendency to retain a new size after the stimulus is removed, and its much slower relaxation compared with the rate of contraction to light, on convergence and, when present, in accommodation.

With regard to cases of "iridoplegia" or "internal ophthalmoplegia" with absent reflexes: the eye signs are almost always unilateral; a history of long standing inequality of the pupils, of recent sudden increase in the size of one of them, perhaps with misty vision, of wide variations in the size of the larger pupil, or the presence of hippus confined to the larger pupil, is decisive. Occasionally tonic reactions in the smaller pupil give the clue. Even if the smaller pupil is normal, or the signs are bilateral, appropriate tests will almost always reveal tonic reactions. To elicit the light reflex it may be necessary to place the patient in a dark room for an hour and then expose the eyes to very bright diffuse light; the light from a pocket torch rarely suffices to start a contraction. To elicit the reaction on convergence persistence may be required on the part of the patient and the examiner; I have seen five and ten seconds elapse before any contraction could be seen. If accommodation is tested in patients with misty vision it will probably be found that the movement though slow is not limited in range. Tonic convergence on accommodation in patients who make no complaint is probably much commoner in this disorder than is recognized at present. Its discovery would clinch the diagnosis, as it is never observed in other conditions.

It may be that tonic reactions would be found in all of these cases if our tests were thorough. I believe, however, that they may be unobtainable in a pupil that has recently increased suddenly in size. If this is so the diagnosis, in patients without changes in the reflexes, may be in doubt for a time; but it can still be made with considerable confidence if the signs are unilateral in a healthy young female otherwise free from signs of organic nervous disease, especially if there is a history of preceding inequality of the pupils.

We have no proof at present that absence of tendon reflexes alone may be a manifestation of this disorder. This diagnosis might be entertained if the signs are of long standing, if other signs and symptoms

of organic nervous disease are missing, and the family history is negative for familial nervous disorders and syphilis.

In the past syphilis of the nervous system was almost always diagnosed or suspected because the tonic convergence reaction in pupils apparently inactive to light was mistaken for the Argyll Robertson phenomenon. So long as the prevailing definition—the pupil reacts on accommodation but not to light—is supposed to define what Argyll Robertson described, the same regrettable mistake will continue to be made. The tonic pupil and the Argyll Robertson pupil have hardly anything in common and should not be confused. Syphilis is usually suspected too in the cases where the pupil appears on superficial examination to be fixed or partially fixed. If efforts to disclose tonic reactions have failed and a careful consideration of all of the features of the case leaves room for doubt, the appropriate tests to exclude syphilis must be made.

Diphtheria can produce ocular symptoms and loss of tendon reflexes. This diagnosis had been suggested in more than one of my cases. It has never been known to cause a tonic reaction on convergence, though its ocular symptoms have been closely studied by many competent observers. The internal ophthalmoplegia of this disease has characters which render it entirely distinct from other forms; there is a true paralysis of accommodation which is almost always isolated and always bilateral; it usually appears about ten weeks after the outset of the disease and complete recovery always occurs in a month or two; it never passes over into tonic accommodation (Axenfeld).

The ocular manifestations of encephalitis lethargica too have been closely studied in recent years; tonic reactions have never been observed. The tonic convergence reaction was well known to ophthalmologists many years before encephalitis lethargica became common. No patient with tonic reactions has ever been known to present any of the recognized early or late symptoms of this disease.

NATURE OF THE DISORDER.

The tonic reaction seems to be the expression of a unique kind of perversion of pupillomotor activity. A stimulus is applied; for a time there is no response; then a contraction begins and continues at an ever diminishing rate but through a range in excess of the normal; once begun this contraction may continue after the stimulus is removed; or having reached its maximum it retains it long after the stimulus has ceased to

act; relaxation then proceeds with even greater slowness than contraction.

The curious manner in which stimuli are stored in excess and slowly emitted points to some change in the activity of the cells in the vegetative portion of the oculomotor nucleus. We are driven to the viscera for analogous types of innervation.

The problem raised by the tendon areflexia is one that we have been forced to consider in relation to other disorders of the nervous system.

We are most familiar with this abnormality as a sign of disease of the spinal cord or peripheral nerves, but we encounter it in a number of conditions in which the central nervous system, apart from the vegetative nervous system, is intact.

In dystrophia myotonica and other myopathic atrophies absence of knee and ankle jerks is seen in patients with powerful unwasted lower limb muscles and intact sensibility. The extra-muscular phenomena in dystrophia myotonica point to a disorder of the vegetative nervous system.

In family periodic paralysis the tendon reflexes may be absent for hours or days. In the intervals there are no organic signs. During the cataplectic attacks in narcolepsy the tendon reflexes are completely abolished. In the cases where narcolepsy is symptomatic of encephalitis lethargica, the common association of obesity and the occasional occurrence of disturbances of sugar and water metabolism, vasomotor and heat regulation and the like indicate the region of the brain whose functions are disturbed.

I have seen complete abolition of the tendon reflexes in a patient with myasthenia gravis at a time when there was no weakness in the limbs.

A young woman who was recently under my care at the National Hospital illustrated the close relation of a number of disorders of the vegetative nervous system to which for convenience we attach distinctive labels. She attended first for severe Graves' disease with all the classical signs; on examination she was found to have in addition almost complete external ophthalmoplegia, tonic pupillary reactions and complete abolition of all the tendon reflexes in the upper and lower limbs. The signs were all present while she was still able to attend as an out-patient; power and sensibility in the limbs were then intact. Some weeks later she entered hospital with severe myasthenia gravis from which she died. Apart from the myasthenic symptoms there were no neurological signs; the Wassermann reaction in the blood was negative and the cerebrospinal fluid was normal in every respect.

Most of these diseases present ocular signs. There can be little doubt that they are all related, more or less closely.

SUMMARY.

The tonic pupillary reaction, under a number of different names, has been known to ophthalmologists since 1902.

In some of their cases absence of one or more of the tendon reflexes was noted, but this was misconstrued as further evidence that the ocular signs were due to syphilis.

My conclusions here are based on a study of nineteen patients with tonic pupils, thirteen of them with absent tendon reflexes, that have come under my own observation, and forty-four published cases of tonic pupil, nine with absent tendon reflexes, that have been reported, almost all, in journals of ophthalmology. The cases with tonic pupils and absent reflexes are tabulated.

The disorder manifests itself in complete and incomplete forms. The complete form is characterized by the presence of the tonic convergence reaction in pupils only apparently inactive to light and absence of one or more of the tendon reflexes. The term incomplete forms is used for cases with (a) tonic pupillary reactions alone; (b) atypical phases of the tonic pupil alone (usually mistaken for iridoplegia or internal ophthalmoplegia); (c) atypical pupils with absent tendon reflexes; (d) absent tendon reflexes alone.

The tonic pupillary reactions are described in detail and discussed in relation to the Argyll Robertson phenomenon, fixed pupils and internal ophthalmoplegia. The conclusion is reached that the tonic pupil is essentially different from them. The features that distinguish it from the Argyll Robertson pupil are emphasized. The incidence and distribution of tendon areflexia is given and the general features of the disorder are described. The age of onset cannot be determined; females preponderate largely; the cause is unknown. The disorder runs a benign course and rarely causes trouble. Occasionally vision is affected by defective accommodation.

Evidence is adduced to show that the disorder is unrelated to syphilis.

The diagnosis is discussed and reference is made to the necessity that sometimes arises for persistence on the part of the patient and the examiner, lest easily recognizable tonic reactions be missed. Under differential diagnosis, syphilis, the ocular manifestations of diphtheria and encephalitis lethargica are mentioned only to show that they never produce the symptoms found in this disorder.

Other conditions are referred to in which the tendon reflexes are lost temporarily or permanently in the absence of disease of the spinal cord or peripheral nerves.

The conclusion is reached that the symptoms described are the manifestation of a disorder of the vegetative nervous system. They are the expression of a kind of perversion of nervous activity of which at present we can form no conception.

REFERENCES.

- [1] ADIE, W. J. *Brit. Med. Journ.*, 1931, **1**, 928.
- [2] *Idem. Ibid.*, 1931, **2**, 136.
- [3] AXENFELD, T. *Klin. Monatsschr. f. Augenheilk.*, 1919, **62**, 59.
- [4] BARKAN, O. *Arch. f. Augenheilk.*, 1921, **87**, 189.
- [5] BEHR, C. *Klin. Monatsschr. f. Augenheilk.*, 1921, **66**, 770.
- [6] BRAMWELL, E. and SINCLAIR. *Scott. Med. and Surg. Journ.*, 1906, 528.
- [7] DIMMER, F. *Klin. Monatsschr. f. Augenheilk.*, 1911, **49**, 332.
- [8] DONARUS, A. *Munch. Med. Woch.*, 1919, **66**, 987.
- [9] GEHROCKE. *Neur. Centralbl.*, 1921, **40**, 99.
- [10] JESS, A. *Klin. Monatsschr. f. Augenheilk.*, 1920, **64**, 114.
- [11] LERPERGER, O. *Ibid.*, 1914, **53**, 241.
- [12] MARCUS, O. *Trans. of the Ophth. Soc. of the U.K.*, 1906, **21**, 50.
- [13] MOORE, F. *Ibid.*, 1924, **44**, 88.
- [14] *Idem. Ibid.*, 1931, **51**, 208.
- [15] MORGAN, G. and SYMONDS, C. P. *Guy's Hosp. Rep.*, 1927, **77**, 13.
- [16] *Idem. Trans. Roy. Soc. of Med.*, 1931, 768.
- [17] NONNE. *Neur. Centralbl.*, 1902, **21**, 1000.
- [18] OLOFF, H. *Klin. Monatsschr. f. Augenheilk.*, 1914, **53**, 498.
- [19] REITZ, W. *Ibid.*, 1925, **74**, 159.
- [20] SAENGER, A. *Neurolog. Centralbl.*, 1902, **21**, 887.
- [21] STRASBURGER, J. *Ibid.*, 1902, **21**, 788.
- [22] WEILL, G., and REYS, L. *Rev. d'oto-neuro-oculist.*, 1926, **4**, 488.

THE PART PLAYED BY THE SYMPATHETIC SYSTEM AS
AN AFFERENT MECHANISM IN THE REGION OF THE
TRIGEMINUS.

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FOREWORD BY CHARLES H. FRAZIER, M.D., SC.D.

IN the Neurosurgical Clinic of the University Hospital of Philadelphia, because of the abundance of material, we have had a vital interest in the nervus trigeminus. We have in our files 1,832 cases of major trigeminal neuralgia and have performed 711 major operations.

We have been concerned for some time with certain forms of sensation which have been conserved or which have appeared after total or subtotal section of the sensory root. With this in mind, I sought the co-operation of Professor Harry Helson who has devoted much time to the investigation of cutaneous sensation.

This research was inaugurated with an entirely open mind as to the possible results. The examinations of the various forms of sensation were conducted by Professor Helson with the meticulous technique known only to those experienced, as Professor Helson is, in the test for the different forms of cutaneous sensation.

Hours were spent on individual cases and, so far as I know, examinations such as these have never been made, after severance of the sensory root of the trigeminus. Altogether fifteen cases were selected at random for this research.

The product of this research may prove to be of great scientific importance. A number of phenomena quite unexpectedly have been revealed. Their significance I am not prepared to evaluate.

Among other things it was observed: (1) that after a period of years sensitivity to deep pressure increased one hundred-fold; (2) that there developed after one or more years a pronounced improvement in the ability to localize a given point; (3) that there was a response to extremely hot stimulus described by the patient as stinging or burning; (4) and, this seems to me of far-reaching importance, this sensitivity to

extreme heat was entirely lost when in addition to section of the sensory root a thoracic sympathectomy had been performed: May not this be offered as evidence supporting the growing belief that the sympathetic system has an afferent as well as an efferent function? Professor Helson's observations follow.

In spite of numerous observations made upon the regions supplied by the trigeminal nerve after total or subtotal section of the sensory root, many questions still remain unanswered concerning the afferent mechanisms by which certain sensations are mediated after destruction of the one nerve commonly supposed to be responsible for all sensations of the face. There must be afferent mechanisms not only for the paræsthesias that sometimes appear after the radical operation for trigeminal neuralgia, but also for the gradual restitution of certain sensory functions which indubitably occurs. That these are not due to regeneration of the trigeminal tract will be readily admitted by all familiar with the technique of the radical operation, which involves sectioning of the trigeminal root central to the Gasserian ganglion. Nor can the sensations described by certain patients under identical and carefully controlled conditions be dismissed with the assumption that they are purely psychogenic in character. In the hope that some further light might be shed upon the afferent system of the head and face, we decided to make an intensive survey of the sensory capacities, not only of the regions deprived of the trigeminal supply following the radical operation for trigeminal neuralgia, but, for purposes of comparison, of cases deprived both of the trigeminal and sympathetic supply after removal of the first and second thoracic ganglia and the intervening trunk.

To make the investigation as accurate and complete as possible we examined a number of patients at various intervals following operation in order to determine if, and to what extent, sensation remains after deprivation of the trigeminal supply and if there is any restitution in sensory function as time goes on. In our examinations we employed the methods of procedure developed by psychologists and others interested in sensation, for only the most meticulous procedure, utilizing measurements wherever possible, can reveal what sensory functions are present and what changes occur in time. Some fifteen patients in all were examined, but only seven were carefully re-examined a number of times over a period of two years. Our re-examinations showed that improvement in certain sensory functions actually occurs, a fact which

will be stressed in this paper since it throws light upon the possible sources of sensation. All of our subjects were cases in which the second and third divisions of the trigeminal root had been sectioned (sub-total section).

Six classes of sensation were intensively studied: light and deep pressure, sensation of cold, warmth and heat, pain, two-point pressure limen, and the ability to localize a spot within the affected area, also called error of localization. Our discussion of each of these functions will show that the face depends chiefly upon the trigeminal nerve for its afferent supply, but as soon as it is deprived of this source some other nerve, either the facial, the sympathetic, or both, takes over some of the functions formerly mediated by the trigeminal and can be held responsible for the sensations found there. Or may it be through anastomosis with the branches of cervical plexus?

Light and deep pressure.—It is well known that immediately after operation there is no sense of light pressure, but that deep pressures are felt with decreasing sensitivity from the borders of the region toward the malar, infra-orbital and oral regions. Except for isolated spots which may be hyperalgesic, stimulation with human hair or straw fails to elicit any sensation when the stimulus is punctiform. Within a year after operation, however, if the hair or straw is *brushed* or *swept* across the face it will be felt. But properly speaking there is never, at any time after operation, any restitution in the sense of light pressure which seems to be mediated exclusively by the trigeminal nerve and is not taken over by any other nerve. The fact that the stimulus is felt when it is swept across the face will be discussed later.

When we come to *deep pressure* the story is different. Up to a month after operation deep pressures are not felt unless extremely heavy; with a pressure of 4,000 grm. upon a dull stimulus, deep pressure will be appreciated. Within a year sensitivity to this form of stimulation has improved to such an extent that a pressure of as little as 20 grm. in the border regions, and 100 grm. in the regions most affected by the operation, will be felt. After four years 20-40 grm. were felt by two patients throughout the entire area formerly supplied by the second and third divisions of the trigeminal nerve. Here there can be no doubt that restitution of function has occurred since sensitivity to deep pressure has increased at least one hundred-fold.

In 1890 Krause [4] reported that after the radical operation for trigeminal neuralgia he had found in his Case 5 some preservation of pressure sensation in certain areas, but only on deep pressure.

Spiller in 1906 [5] in ignorance of Krause's statement, recorded briefly that in two cases in which the Gasserian ganglion had been removed, he had found that the pressure sensation was preserved, although all other forms of sensation were lost, and was probably the first to attribute the pressure sensation to the nervus facialis. His clinical notes and findings were reported in detail by two of his students, Ivy and Johnson [3], with the definite statement that the seventh nerve conveys fibres of deep or pressure sensibility. Spiller discusses more in detail the preservation of deep pressure sensation after removal of the Gasserian ganglion in his paper on "Tumor of the Gasserian Ganglion," published in 1908.

Temperature.—At all times after the operation temperatures between 15° and 45° C. fail to evoke sensations of cold, warmth or heat. The medium range of temperatures goes when the sensory root is cut, and never returns. However, if an extremely hot stimulus, one between 60° and 75° C., be applied to the malar or oral regions, most patients will report a stinging or pricking sensation. They never used the word "hot" if it were carefully concealed from them that the steel cylinder had been heated. One paradoxical result deserves mention since it was verified on two patients independently, and shows that the new nerve responding to this form of stimulation has not learned its lesson well, so to speak; these subjects reported that a stimulus of 55° C. (ordinarily hot) was cold in the malar region, whereas stimuli normally giving cold failed to be reported as such when applied. To check a suspicion that the sympathetic fibres might be responsible for the responses to extremely hot stimuli, we tested three patients upon whom a thoracic sympathectomy had been performed as well as the radical operation, and we found that they failed to get anything but neutral pressure from the hot cylinders throughout the whole distribution of the trigeminal nerve. One could sear the skin of these latter subjects without getting any response except pressure, while the other patients in whom the sympathetic was not divided reacted very violently if the cylinders were kept on the face more than a few seconds. One perhaps is not surprised that intense heat is described as a stinging or pricking sensation, whereas cold is not felt at all because of the very close association of heat and pain sensations, as seen especially in causalgia. These facts argue for sympathetic participation in some of the sensory functions of the face, at least after the trigeminal supply is gone. No sensations of cold have ever been reported to us even with the application of ice to the operated region, although many patients

report a dislike of cold water or draughts on the affected side of the face.

Pain.—Here we find little or no sensitivity either immediately or as long as six years after operation. As a stimulus we used a needle with 30 grm. pressure which elicits a report of pain on the normal side. This is felt merely as a dull, blunt pressure. We therefore might conclude that normally the trigeminal nerve alone mediates the pain sense and this function is not taken over by any other nerve. But there are a number of phenomena which seem to show that there is some pain supply in the face after the trigeminal nerve is gone. Some patients complain of spontaneous pains within the operated region, usually in isolated spots. If these spots are touched rather lightly they over-react as if they were hyperalgesic. At the very time that patients complain of spontaneous pains stimulation of the regions concerned often fails to evoke anything more. This fact may be due to the relatively light stimulation which does not penetrate to the deeper-lying tissues and nerves. It must be remembered that the reactions to the extremely hot stimuli occurred only after sufficient time was given to penetrate below the surface. Our inability to evoke pain in the trigeminal region with the 30-grm. needle may be due to the fact that we have not reached the deeper-lying mechanisms possibly responsible for paræsthesias.

TABLE I.—IMPROVEMENT IN ABILITY TO LOCALIZE A SPOT TOUCHED WITHIN THE TRIGEMINAL DISTRIBUTION AFFECTED BY OPERATION.

Patient	Time since operation	Error of localization	
		Operated side	Normal side
D.	6 years	8.57 ± 5.39 mm.	4.09 ± 2.20 mm.
H.	2 months	10.12 ± 5.57	5.73 ± 4.59
	11 months	8.06 ± 5.10	
M.	5 months	14.17 ± 11.90	4.81 ± 2.48
	13 months	12.95 ± 9.50	
Pe.	3 years 1 month	12.30 ± 6.98	3.78 ± 2.17
	4 years 8 months	12.37 ± 9.25	
Po.	5 months	11.38 ± 8.34	4.66 ± 3.38
	12 months	10.82 ± 4.96	
V.	3 weeks	18.50 ± 11.10	4.50 ± 2.35
	9 months	9.09 ± 5.50	
Y.	10 months	11.19 ± 6.26	4.42 ± 2.27

Localization.—We find the most pronounced improvement in the ability to localize a spot touched within the operated area. This follows from, and is a check upon, our earlier finding that sensitivity to deep pressure improves remarkably. In Table I will be found the average error of localization with its standard deviation at various intervals since

operation for the operated side of the face and for the normal side. The most striking case is that of patient V, who shows an error of localization of 18.50 mm. three weeks after operation, as compared with an error of 9.09 mm. nine months after operation. It looks as if some other nerve is "learning" the function formerly mediated by the trigeminus. The table shows that improvement occurs rapidly during the first year after operation and then proceeds more slowly for a year or two, after which a stationary state is reached wherein ability to localize is still far from normal, but definitely better than immediately after operation. The change from absolute inability to localize a spot within the trigeminal region to an error only twice as great as the normal error is most striking indeed. Whether we are dealing here with vicarious functioning of the seventh nerve for the fifth or sympathetic involvement, we shall discuss later.

Two-point limen.—By this is meant the ability to discriminate two points as two. This function, an epicritic function according to Head and his co-workers, is irretrievably lost with the trigeminal because two points of the æsthesiometer, no matter how far apart, applied within the trigeminal distribution are felt as one, if felt at all. When asked where the one point is felt, the patient sometimes chooses a spot between the two spots actually stimulated or one or the other of the spots touched.

Except for light pressure, pain (?), medium range of temperatures and two-point limen, there certainly appears to be restitution of certain sensory functions in the regions formerly served by the trigeminal nerve. The retraction of the border regions, improvement in ability to sense deep pressures, to localize spots, to feel extremely hot stimuli, and a generally heightened sensitivity in the region force us to assume that peripheral neural mechanisms are present to mediate these. We can say either that the facial nerve alone is responsible, since it is known to carry some sensory fibres; that the sympathetic nerve also has sensory functions which appear when the trigeminus is gone; that an anastomosis has been established with the cervical plexus; or that all three nerves are playing a part in the new sensory picture we have delineated after trigeminal resection.

It is easy to assert that the facial nerve is alone responsible for all of these sensory functions, except for the fact that in the cases where the sympathetic supply was gone as well as the trigeminal but the facial remained, there was no response to extremely hot stimuli anywhere in the region. Furthermore, the fact is well known that

temperature reactions are closely associated with the contractions of muscles supplying the veins and arteries, a fact which the "temperature spot" theories of temperature sensations have tended to neglect but which is most important in showing their relations to the sympathetic system. The intense dislike of, and shrinking from, cold air and water exhibited by many patients after the radical operation appears very much like a total reaction characteristic of sympathetic functioning, for it is only when the whole face is affected by cold that the disagreeable feelings are reported, since the application of ice in a punctiform manner failed to elicit unpleasantness. The fact noted above that in order for a light touch to be felt the hair or straw must be swept across the skin, argues for some afferent mechanism whose functions are more diffuse and totalized than usually associated with peripheral cutaneous nerves. We are therefore forced to conclude that we have here *bona fide* evidence for the rapidly growing belief that the sympathetic and parasympathetic systems have afferent as well as efferent functions.

It is hardly necessary to point out the rich supply of sympathetic fibres to the face—fibres from the internal carotid plexus to the Gasserian ganglion, from the ciliary, sphenopalatine, otitic, and submaxillary ganglia. As Frazier [2] has previously said: "These rich sympathetic connections may not be without their significance. Operations upon the cervical sympathetic ganglia have been practised for many years for the purpose of relieving pain, as in trigeminal neuralgia and migraine . . . when one stimulates electrically the cervical sympathetic ganglion or the periarterial sympathetic plexus of the common carotid artery . . . the patient frequently complains of pain within the zone of the trigeminal distribution."

By means of this assumption, that the sympathetic has an afferent as well as an efferent function, we find ourselves in a better position to understand the sensations which remain and develop after section of the sensory root of the trigeminus. Our findings support the conclusions reached by Foerster, Altenburger and Kroll [1] that the sympathetic plays a sensory role in every part of the body, and that to de-afferent a region completely the sympathetic supply must be taken away as well as the peripheral nerve supply commonly supposed to mediate cutaneous sensations. Owing to the numerous sources of sympathetic supply, it is most difficult to be sure from purely operative procedures alone when a complete sympathectomy has been achieved. Our investigations of the sensations in the face after loss of both the trigeminal and sympathetic supplies shows a different state of affairs from that seen when only the

trigeminal supply alone is lost. The sensory functions of the sympathetic appear (or may even develop) when the masking effect of the trigeminal disappears, because we certainly find further loss in sensation when, in addition, the sympathetic supply is taken away. The absolute zero of cutaneous sensitivity can be reached not merely through resection of the peripheral nerve supply (trigeminal and intermedius) but requires deletion of the sympathetic supply as well. We may here have the key to that class of neuralgias called "atypical" from the point of view of traditional theories of nerve functioning.

REFERENCES.

- [1] FORSTER, ALTENBURGER und KROLL. "Ueber die Beziehungen des vegetativen Nervensystems zur Sensibilität," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1929, **121**, 139.
 - [2] FRAZIER, O. H. "Pain Phenomena of the Face, their Origin and Treatment, with Special Reference to Trigeminal Neuralgia," *Amer. Journ. of Med. Sci.*, 1925, **169**, 469.
 - [3] IVY and JOHNSON. "Preservation of Deep Sensibility of the Face after Destruction of the Fifth Nerve," *Univ. of Pennsylvania Med. Bull.*, 1907, **20**, 85.
 - [4] KRAUSE. "Die Neuralgie des Trigeminus," Leipzig, 1896.
 - [5] SPILLER. *Journ. Nerv. and Ment. Dis.*, 1906, **33**, 736, also "Tumor of the Gasserian Ganglion," *Amer. Journ. of Med. Sci.*, 1908, **136**, 712.
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ON SUPRASellar CHOLESTEATOMAS.¹

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THE chiasmal syndrome and its variations are now fairly well known, thanks mainly to the work of Harvey Cushing. The more common types of suprasellar lesions may thus be readily recognized before operation in the majority of cases. Diagnostic errors are, however, easily committed when the lesion is of some more unusual histological type, or when the nature or extension of the pathological changes is variable, as in cisternal arachnoiditis. That cholesteatomata, when arising in the suprasellar region, may occasion a peculiar variation of the chiasmal syndrome, which seems to be sufficiently characteristic to enable a correct pre-operative diagnosis, is shown by the following two cases.

Case 1.—G. M., female, aged 19, Surgical Clinic, Serafimerhospital No. 138/31.

Apart from a birth palsy (plexus injury) of the right arm the patient had always been in good health until August, 1925, when she began to have double vision. This persisted for a month and then disappeared. At the same time she noticed that she could not see as well as previously. Otherwise there were no symptoms, no headache or vomiting, and after the double vision had disappeared the patient felt perfectly well apart from her declining vision. In May, 1926, she consulted an eye specialist because she could not see well enough to read without glasses. At this examination it was found that she was blind in the right eye, and that vision in the left eye was reduced to 0.4. The fundi showed a primary optic atrophy of an extreme degree. She was given antisyphilitic treatment for two years. During this time vision in the left eye remained practically stationary, but there was a slowly progressing constriction of the visual field from the temporal side. She was sent here in July, 1930, by Dr. Dymling, with the diagnosis of suprasellar tumour, but when she was advised to enter the hospital for observation she returned home and did not appear until January 23, 1931.

When the patient entered the hospital her only complaint was that she could not see well and she thought that a further decrease in visual acuity had

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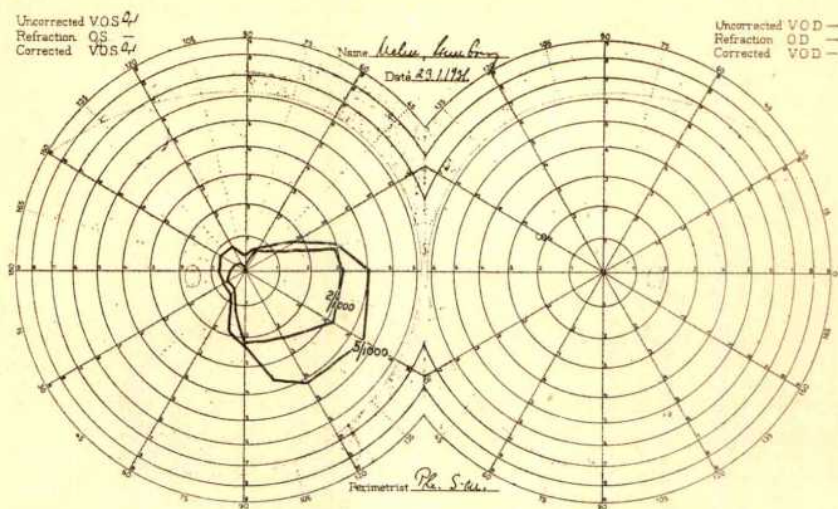


FIG. 1 (Case 1).—Visual field before operation.

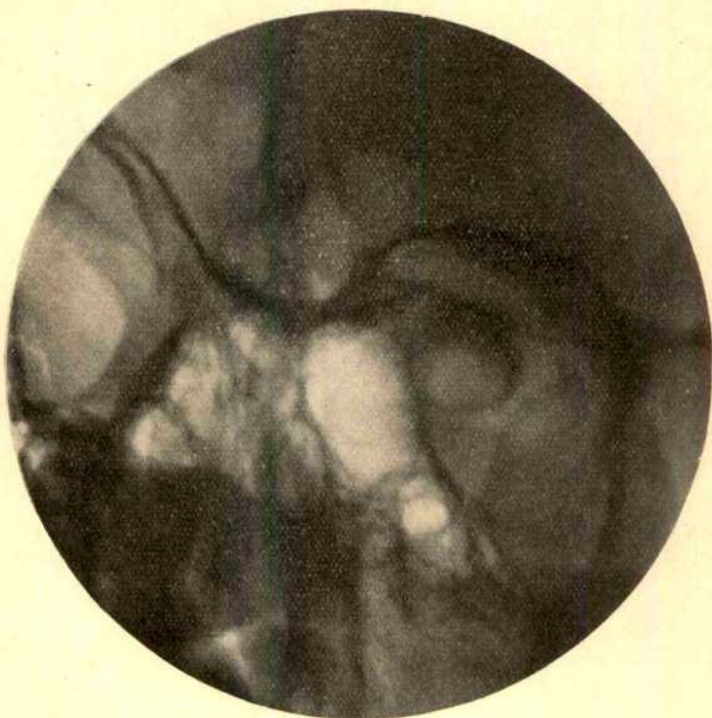


FIG. 2 (Case 1).—Right optic foramen.

taken place since July, 1930, when it had been found to be 0.4 in the left eye. She was a slender but normally developed girl of 19. Menstruation started at the age of 13, and had been normal ever since. Her skin was fine in texture but within perfectly normal limits. Secondary sex characteristics were normally developed. Hair was normal in texture and distribution. Her basal metabolism was + 34.

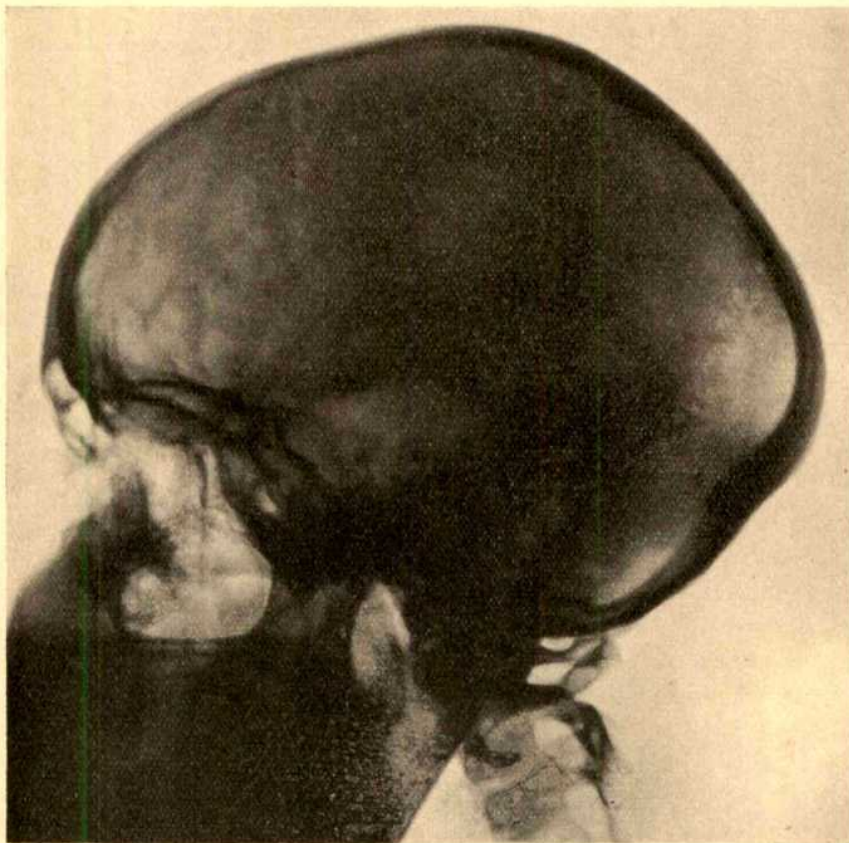


FIG. 3 (*Case 1*).—The sulcus chiasmatis of the sphenoid bone is very much enlarged and is about three times as wide as normal. The anterior clinoids also show some pressure absorption.

Examination of the eyes showed both pupils to be wide but reacting to light, though very sluggishly in the right eye. The right eye was blind and visual acuity in the left eye was reduced to 0.1. Examination of the visual field showed that only the lower nasal quadrant was left (fig. 1). The macular region was spared. The fundi showed a primary optic atrophy of an extreme degree. Both discs were chalky white with sharp margins. The vessels seemed to be normal.

Neurological examination otherwise was entirely negative. Roentgen examination of the head (Dr. Lysholm) showed that both optic foramina were wider than normal and measured about 6 to 7 mm. in diameter (fig. 2). The sulcus chiasmatis of the sphenoid bone (fig. 3) was very much enlarged. The sellar region otherwise was essentially normal as well as the rest of the cranium. No suprasellar calcifications could be detected although such changes naturally were searched for with particular care, and no bony prominence in the region of the tuberculum sellæ suggestive of a meningioma could be seen.

That a compression of the optic chiasma was present in this case could hardly be doubted in view of the primary optic atrophy, the field defects and the slowly progressive character of the lesion. Since, however, the clinical picture did not fit in with any of the known variations of the chiasmal syndrome, the nature of the lesion was difficult to determine. In view of the age of the patient, a craniopharyngioma seemed to be the tumour most likely to be expected, even though suprasellar calcifications were absent. The complete absence of disturbances of pituitary function was difficult to reconcile with this diagnosis, since some degree of pituitary insufficiency is almost always present in cases where the optic atrophy has reached a high degree, and is usually very marked in cases of this type. It is also very unusual to see a craniopharyngioma without even a trace of deformity or pressure absorption of the posterior clinoids, and in most cases where pressure on the optic chiasma has been sufficiently marked to cause pallor of the discs to an appreciable degree the roentgenological changes of the sella are outspoken. The unusual widening of the optic foramina naturally focused attention on the possibility of a glioma of the chiasma, but these tumours sooner or later come to involve the floor of the third ventricle, and in the absence of any evidence of extension of the lesion to this region, in spite of the long duration of the malady, a glioma of the chiasma was thought to be a very remote possibility. A suprasellar adenoma or a meningioma from the tuberculum sellæ were the favoured diagnostic possibilities, but in both cases the age of the patient was considered to be an argument of considerable weight against this diagnosis. The widening of the optic foramina was difficult to explain as caused by any of these lesions, but we were then inclined to discount this finding and regard it as accidental. The widening of the sulcus chiasmatis might have been caused by a suprasellar meningioma, which therefore was regarded as perhaps the lesion most likely to be found.

Operation, January 29, 1931. Under local anæsthesia a right-sided trans-frontal flap was turned down and the chiasmal region explored. After the

dura had been opened along the lesser wing of the sphenoid neither optic nerve could be seen. The space above and anteriorly to the optic nerves was occupied by a mass of a pale whitish-yellow colour which completely concealed the chiasma and both optic nerves. After the mass had been incised the soft cheese-like contents of a typical cholesteatoma began to extrude. The cholesteatomatous masses were included within a thin capsule which on the inside had a velvet-like appearance with thin layers of glistening pearly matter

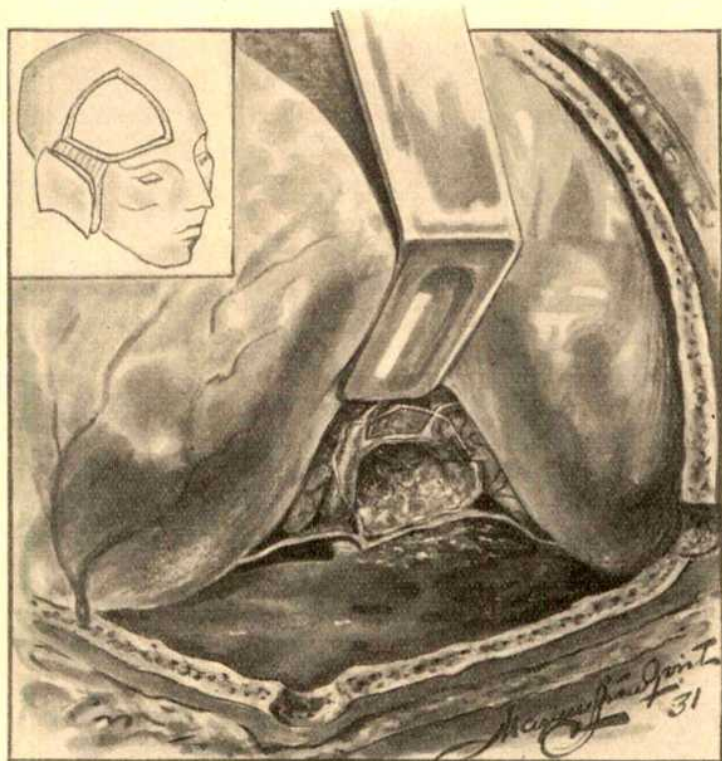


FIG. 4 (Case 1).—Sketch of the field of operation. The contents of the tumour have been cleared out and the arteries on the base of the brain can be seen through the thin capsule.

adhering to it in places. After most of the cholesteatomatous masses had been cleared away with a suction apparatus all the big vessels on the base of the brain could be seen through the thin capsule (fig. 4). As is usually seen in cholesteatomas the capsule insinuated itself into every cleft and crevice of the neighbourhood in the form of multiple spurious herniations filled with cholesteatomatous matter. The optic nerves could not be seen. They were probably flattened out and plastered to the underside of the capsule and it was not thought wise to search much for them as they might easily be damaged in

the procedure, as we learned in the following case where a more radical procedure was adopted. For the same reason, and because the capsule was found to be somewhat adherent to the blood-vessels, no attempt was made to remove the capsule, of which only a slip was taken for examination. The cavity, which was approximately the size of a golf-ball, was filled with salt solution and the wound closed without drainage.

Microscopical examination (Professor Bergstrand) of the tissues removed at operation showed the tumour to be a typical cholesteatoma. The healing of the wound was perfect and convalescence undisturbed except for a mild transitory polyuria, which however never exceeded 2,000 c.c. per twenty-four hours. The patient was discharged on February 18, with visual acuity and field practically unchanged. In June, 1931, she reported herself to be in excellent health and her vision had improved to 0.3, although the visual field was unchanged.

The second case came under observation within a few days of the first, which naturally greatly facilitated a correct pre-operative diagnosis.

Case 2.—E. E., a female, aged 27. Surgical Clinic, Serafimerhospital, No. 128/31.

Since the age of 9 the patient had suffered from headache coming on in attacks usually once or twice a week. The headache was at first localized over the right eye and in the right temple, radiating towards the right occipital

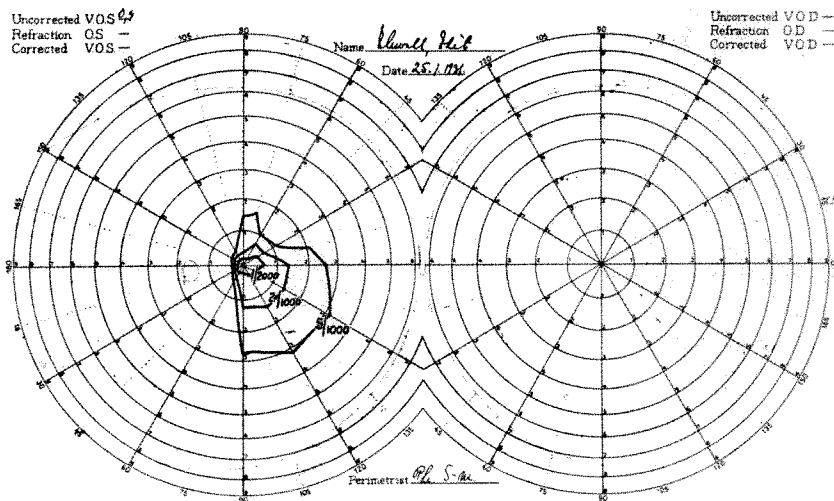


FIG. 5 (Case 2).—Visual field before operation.

region. After the right eye had become blind five years previously the headache had been less severe, had not occurred so often and had been more localized to the corresponding regions on the left side. The headache had never been very

severe and could always be entirely relieved by aspirin. There had never been any vomiting. In 1926 the patient noticed that she was almost blind in the right eye, and an eye specialist whom she consulted at that time found that vision in the right eye was reduced to light perception in the nasal part of the field while the left eye was normal. A year later she was completely blind in the right eye. In September, 1930, the patient noticed a decrease of visual

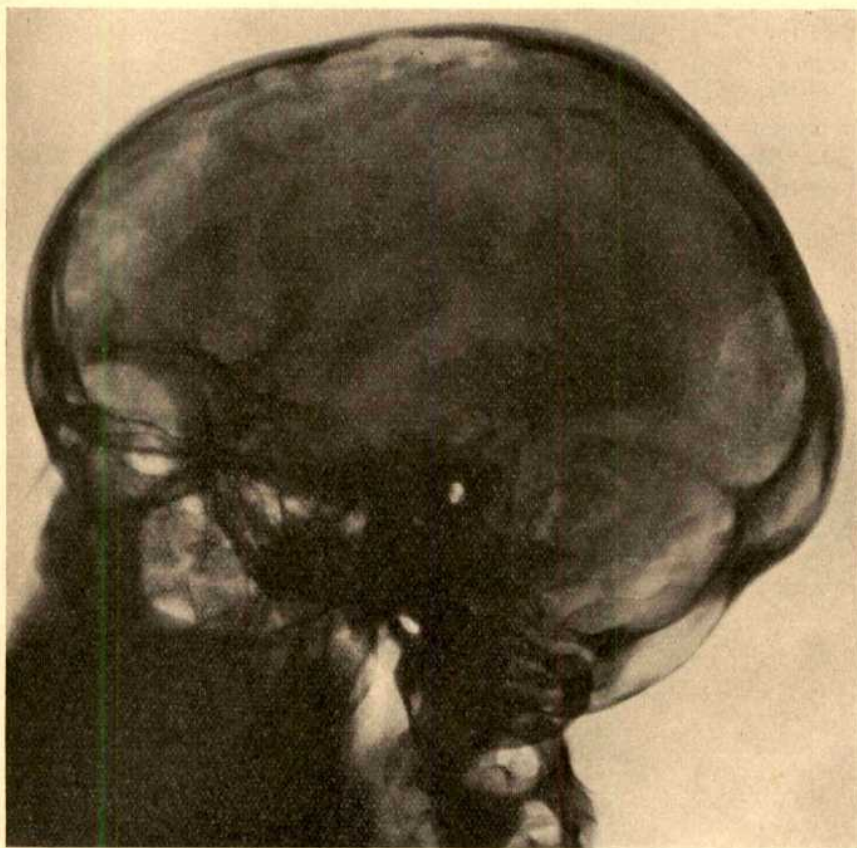


FIG. 6 (Case 2).—Enlargement of the sulcus chiasmatis less marked than in the preceding case. Marked pressure absorption of the right anterior clinoid process.

acuity in the temporal field of the left eye which progressed so that after a few months this part of the field was completely blind. She then consulted Dr. Raeder in Oslo, who, on January 21, 1931, referred her to me with the diagnosis of suprasellar tumour.

The patient was a normally developed woman who had always menstruated regularly. The skin was normal in texture. Distribution of hairs was also normal. The basal metabolism was + 4 per cent.

There was a slight convergent strabismus of the right eye, otherwise movements of the eyes were normal. The right pupil did not react to light. The left pupil reacted normally to light and accommodation. The right disc was chalky white with sharp margins and narrow arteries. This eye was completely blind. In the left eye vision was 0'9. The disc was definitely pale, especially in its temporal part, and the arteries narrow. Examination of the left visual field showed a result which was identical with the one obtained in Case 1, i.e., integrity of the macula and of the lower nasal quadrant. However, with the smaller test objects even this quadrant showed a considerable degree of constriction (fig. 5).

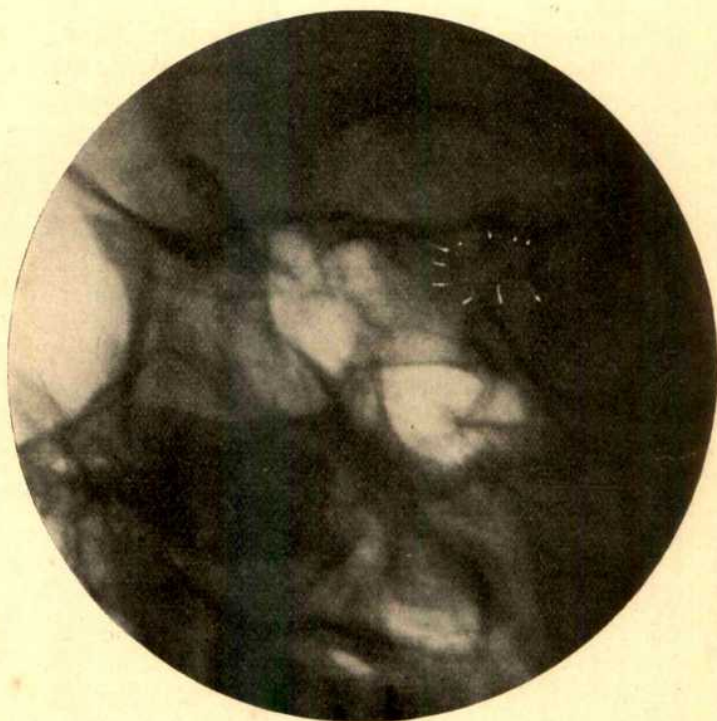


FIG. 7 (Case 2).—Right optic foramen very much enlarged and of irregular form with pressure absorption of its margins.

Neurological examination was otherwise completely negative. Roentgenological examination of the head (Dr. Lysholm) disclosed a condition very similar to that in the preceding case, though somewhat more pronounced. The right anterior clinoid process showed a thinning of its central part, merging with a definite erosion of the bone on the mesial and anterior aspect of the process (fig. 6). The right optic foramen was much larger than the left (fig. 7). Otherwise the sella and the rest of the skull were essentially normal, though there was perhaps some slight convolutional atrophy.

Both with regard to history and clinical findings, this case was almost an exact replica of the first, and a pre-operative diagnosis of suprasellar cholesteatoma did not seem to involve much chance of error.

Operation I, February 2, 1931. A right transfrontal flap was turned down under local anaesthesia. The operative findings were exactly similar to those in the preceding case. After the capsule had been incised and the cholesteatomatous masses evacuated one saw the same picture of a thin velvet-like membrane covering the base of the brain and the big vessels. When these were touched with the suction apparatus in the process of cleaning out the contents the patient complained of severe pain in the head. An attempt was then made to identify the optic nerves, which of course was a necessary preliminary to any attempt to remove the capsule. After some search the right optic nerve was identified as a thin greyish strand entirely surrounded by cholesteatomatous masses which seemed to have grown all around it. The left optic nerve could not be seen and further attempts to expose it or to remove the capsule were abandoned for fear of injury to the nerve. As events proved this must nevertheless have been inflicted. Probably the left nerve was, like the right one, completely surrounded by the cholesteatomatous masses and must have been injured or torn during the attempt to expose it, or during the process of cleaning out the contents of the tumour. Only a fragment of the capsule was removed for examination. The cavity, which was of the same size as in the preceding case, was filled with salt solution and the wound closed without drainage.

Microscopical examination (Professor Bergstrand) of the removed part of the capsule showed the tumour to be a typical cholesteatoma.

When vision was examined immediately after operation it was found that the patient was blind. She claimed to have light perception but could not count fingers. As later examinations showed her to be completely blind it is probable that her light perception was imaginary.

Her convalescence was uneventful except for occasional headaches and an unusually slow pulse. The wound healed without reaction and she was discharged on February 25.

A few days later she re-entered the hospital after having had very severe headaches for a few days and high temperature. On examination she was found to have a temperature of between 39° to 40° C., and complained of very severe headache. The flap was not elevated and it was somewhat difficult to explain her condition as there was no sign of wound infection. As long periods of hyperpyrexia and increased intracranial pressure are sometimes seen after operation for cholesteatoma, it was thought that a reaction of this type had occurred. Her pressure symptoms seemed to be so urgent that re-elevation of the flap was indicated.

Operation II, March 3, 1931. Under local anaesthesia the old flap was again elevated. The dura was exceedingly tense. After the frontal lobe had been elevated it was found that the opening in the capsule was closed by

adhesions and when these were separated a large amount of thick greyish-yellow pus escaped. Immediate smears showed no micro-organisms. Cultures were taken but these proved to be negative. The cavity was rinsed out with salt solution and the wound closed without drainage.

The case obviously was one of aseptic suppuration caused by the desintegration of cholesteatomatous matter which had been left in the cavity. Similar reactions do not seem very uncommon after operations for cholesteatomas. Critchley and Ferguson [1] mention the occurrence of post-operative febrile reactions in some of their cases. Several years ago I had a case of cholesteatoma in the lateral ventricle where removal of the tumour was followed by a period of hyperpyrexia of several weeks duration, with increased intracranial pressure and turbid, though sterile, fluid in the ventricle from where the tumour had been removed. In another case I observed a fatal aseptic meningitis from spontaneous perforation of a fourth ventricle cholesteatoma. In the present case, wound healing occurred without reaction and the patient was discharged on April 16. Her health has since remained good, but she is completely blind.

The clinical features of the two cases presented above are almost identical. In both cases a chiasmal syndrome of a type unusual for the age of the patients was found. Although suprasellar cholesteatomas, of course, may cause other variations of the chiasmal syndrome, the striking similarity of the clinical features in the two cases just described seem to warrant the conclusion that when the following symptoms are present a diagnosis of suprasellar cholesteatoma may be ventured upon with reasonable certainty :—

(1) A very slowly progressive primary optic atrophy with bitemporal hemianopia occurring in a young person.

(2) An essentially normal sella turcica, but with widening of one or both optic foramina and pressure absorption of one or both anterior clinoids and of the sulcus chiasmatis of the sphenoid bone.

(3) Complete absence of signs of pituitary insufficiency.

The syndrome of suprasellar cholesteatomas, therefore, is in many respects very like the one caused by meningiomas of the tuberculum sellæ, but differs from this syndrome in that it occurs at an age when meningiomas are rare. Furthermore, widening of the optic foramina does not occur with meningiomas, and the widening of the sulcus chiasmatis probably very rarely attains a degree comparable with that observed in Case 1. In the stage when the optic atrophy is as advanced, as in the cases cited above, some degree of pituitary insufficiency is to be expected in the case of a meningioma.

The variations of the chiasmal syndrome caused by different tumours depends upon the size and exact localization of the growth, the age of the patient and the consistency of the tumour.

The cholesteatomas differ from other tumours in this region in several of the above-mentioned respects. They are congenital tumours and therefore symptoms are likely to occur at an early age. Among Critchley and Ferguson's [1] cases the average age of the patients was 37 years, although among their eight cases the average age of the patients was much influenced by the unusual fact that one patient was 73 years old when symptoms first occurred. In my own experience of five cholesteatomas none of the patients was above 32 years when symptoms occurred and the average age was 27. The cholesteatomas are very slowly growing tumours and in the suprasellar region the onset of symptoms is likely to be very gradual. Probably no other tumour in the suprasellar region except the craniopharyngioma is of such a slow growth as the cholesteatoma. The consistency of cholesteatomas is softer than that of any other tumour of the suprasellar region, excepting possibly the adenomas, but even here the more rapid growth of this tumour usually causes a greater degree of tension within the capsule and consequently gives the growth a firmer consistency. Occasionally the craniopharyngioma has a thin soft capsule, though rarely of the same degree as the cholesteatoma, but the fluid within the capsule is usually under considerable tension, which gives the tumour a comparatively firm consistency. It is easy to understand that the surrounding structures easily adapt themselves to the slowly growing cholesteatomatous mass enclosed under little or no tension within its soft capsule, and that in this particular situation the optic nerves are the only structure which cannot evade pressure from the expanding growth. As long as the cerebrospinal fluid pathway is not occluded the intracranial pressure need not be affected. Absorption of bone therefore does not occur except where the cranium is immediately adjacent to the tumour. Thus in cholesteatomas of the cerebral convexity pressure absorption, as shown by Cushing [2] and by Schüller [3], is limited to the bone immediately underlying the tumour and is usually so sharply limited to this part that a diagnosis of the nature of the growth can be made from the appearance of the absorption of bone alone. Probably the sellar diaphragm effectively protects the pituitary body from pressure of the overlying soft tumour, which explains the absence of pituitary manifestations. The blood supply of the surrounding part of the brain is not interfered with, since the arteries do not become compressed but instead

indent the soft tumour. The widening of the optic foramina is explained by the tendency of cholesteatomas to crowd their way into every cleft and crevice of the neighbourhood. In Case 2 where the right optic nerve was identified it was accompanied into the optic foramen by a projection of the tumour.

The peculiar variation of the chiasmal syndrome observed in the two cases described above can therefore be regarded as determined by the characteristic features of the tumour with regard to age of onset of symptoms, rate of growth and consistency. This leads me to conclude that we are dealing, not with a merely accidental resemblance of symptoms in two cases, but that a similar syndrome may be expected in most cases of a tumour of this kind in this situation. Naturally, variations may occur when the tumour happens to be more laterally or posteriorly placed in relation to the chiasma, but even so the principal features of the syndrome should be preserved although the field defects may assume a different type.

With regard to the treatment of these lesions my experience in Case 2 leads me to advise against too much searching for the optic nerves and against any attempt to remove the capsule except in cases where the anatomical relations of the chiasma and other important structures are perfectly clear. In every case of cholesteatoma which has come under my observation the capsule has had intimate relations with a number of large blood-vessels and is apt to have so many herniations into clefts and crevices, where the anatomical relations to neighbouring structures are not clear, that it appears that an attempt to remove the capsule is rarely justified. Nor does the very slow growth of these tumours encourage any hazardous attempts to remove the capsule. In my experience the mere clearing out of the contents of the tumour, leaving the capsule intact, as can be done with very little risk, has been followed by excellent results. Two cases operated on according to this method are living and well 6 and 5 years after operation. A conservative attitude towards these lesions therefore seems to be the wisest policy and I would rather take the chance of a second operation some years later than risk life or serious disability of the patient in an attempt radically to remove the capsule. A measure which may possibly be contemplated in cases where the growth has sent a projection into one or both optic foramina is to remove the dorsal margin of the optic foramen in order to relieve the optic nerve from pressure within the foramen. This manoeuvre might also facilitate the identification of the optic nerves.

SUMMARY.

Two cases of suprasellar cholesteatoma are described. The following variation of the chiasmal syndrome may probably be regarded as typical of suprasellar cholesteatomas:—

- (1) A very slowly progressing primary optic atrophy with bitemporal hæmianopsia occurring in a young person.
- (2) A sella turcica essentially normal, but with widening of the optic foramina and the sulcus chiasmatis of the sphenoid bone.
- (3) Complete absence of pituitary manifestations.

REFERENCES.

- [1] CRITCHLEY and FERGUSON. *Bram*, 1928, **51**, 884.
 - [2] CUSHING. *Surg. Gyn. and Obst.*, 1922, **34**, 557.
 - [3] SCHÜLLER. International Neurological Congress, Berne, 1931.
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NOTICES OF RECENT PUBLICATIONS.

The Selected Writings of John Hughlings Jackson. Vol. II. "Evolution and Dissolution of the Nervous System—Speech—Various Papers, Addresses and Lectures." Edited by JAMES TAYLOR, with the assistance of GORDON HOLMES and F. M. R. WALSH. London: Hodder and Stoughton. 1932. Pp. 500. Price 25s.

In the opening paragraph of the paper with which this volume of his writings begins, Hughlings Jackson quotes from Herbert Spencer as follows: "Every science begins by accumulating observations, and presently generalizes these empirically; but only when it reaches the stage at which its empirical generalizations are included in a rational generalization does it become developed science."

The quotation is a singularly appropriate introduction to a volume which, in fact, contains Jackson's "rational generalization" of the numerous clinical observations contained in his writings. This generalization is expressed in his statement of the evolution and dissolution of function in the nervous system. Throughout his writings on epileptiform convulsions, on paralyzes and on disturbances of the speech we see him marshalling the facts of observation until his "rational generalization" emerges inevitably from them. It is in his Croonian Lectures of 1884 that his views are perhaps most clearly and concisely expressed, and it is here that he most brilliantly shows the essential modernity of his outlook.

In that striking work, "Science and the Modern World," Professor Whitehead speaks of the characteristic attitude of the modern mind resulting from the growth of science, and he describes this attitude in terms that may fittingly be applied to the thought of Hughlings Jackson. He says: "This new tinge to modern minds is a vehement and passionate interest in the relation of general principles to irreducible and stubborn facts. All the world over and at all times there have been practical men, absorbed in 'irreducible and stubborn facts'; all the world over and at all times there have been men of philosophic temperament who have been absorbed in the weaving of general principles. It is this union of passionate interest in the detailed facts with equal devotion to abstract generalization which forms the novelty in our present society. . . . This balance of the mind has now become part of the tradition which infects cultivated thought. It is the salt which keeps life sweet."

In no medical writings of our time is this balance of mind so strikingly exhibited, and it is in his combination of acute clinical observer and penetrating discoverer of general principles that Jackson stands out above all other masters in the history of neurology.

While it is probable that there is no observed disorder of nervous function

not comprehended within the scope of his conception of evolution and dissolution of function, it cannot be denied that the task of assessing the place within his scheme of some newly observed phenomenon of disordered function demands from the student of neurology some tincture of the power of abstract thought so richly displayed by Jackson. It is scarcely surprising, therefore, that not all attempts in this direction have been conspicuously successful. The identification of the phenomena of release and their differentiation from those of defect may be relatively simple in the case of some high level dissolution; such, for example, as we see in a case of residual hemiplegia. It is examples of what Jackson spoke of as "local dissolution" at lower levels that present the greatest difficulties of analysis. The phenomena of cerebellar ataxy provide a striking case in point. Here the disorder of motor function is the algebraical sum of the activities of all the surviving components of the nervous motor mechanisms, and the detection and analysis of the negative, or defect, elements in the clinical picture have proved a task of almost insuperable difficulty. Yet no serious student will deny that within the limits of Jackson's hypothesis an adequate analysis is to be found.

His views upon the evolution of function in the nervous system should also act as a wholesome corrective of much loose thinking current upon this subject. Jackson is primarily concerned with what he terms "internal evolution" of function within the higher levels of the individual nervous system, and his writings contain no facile speculating in the realms of phylogenesis, such as is too common in modern neurological theorizing. Founded, as all his generalizations are upon the solid basis of accurate clinical observation, it is clear that speculations of this order could make no appeal to him.

In some measure, possibly, the undoubted complexity of much of Jackson's writing has stood in the way of a more extended and successful application of his views, but a more important factor is probably the limited capacity for generalization and for abstract thought displayed by some even of the most competent clinical observers. Some factor of this order has led a recent writer to declare that hitherto the application of Jackson's teaching has been fruitless in the interpretation of clinically observed phenomena, and it is easy to find illustrations in the literature that may seem to lend colour to this view.

Nevertheless, we may confidently assert that wherever the laws governing the dissolution or function, as formulated by Jackson, may seem to fail us in interpreting the phenomena of disease, the failure lies not in any lack of validity of these laws, but in a lack of understanding of them.

In referring to the difficulty inherent in the study of much of Jackson's writing, it must of course be borne in mind that in breaking new ground in thought and in formulating new conceptions, the pioneer labours under handicaps which are absent from the treading of familiar paths of thought. Human speech is not a perfect instrument, and Jackson had at call neither a generally accepted neurological terminology to lend brevity to his exposition, nor a developed science of physiology to lend him aid. Yet if his lack of a scientific nomenclature sometimes renders his writing lengthy and not easy

to follow, it has at least the merit that with due study any intelligent student may follow his thought without needing that glossary of terms that has become an indispensable item in the equipment of the reader of much modern writing on neurological subjects. Complex as his phraseology is, Jackson found the English language adequate to all he had to express. His pages are not littered with tags from foreign tongues, nor do they carry the dubious adornment of innumerable and superfluous new-coined words to express what simple English words could as tersely and clearly convey.

The full fruit of Jackson's teaching will be long in the gathering, but in placing these two volumes before the present generation of neurologists Dr. Taylor has brought the harvest nearer and has, we may hope, made its promise as bountiful as Jackson could himself have wished. But those also of an older generation who had the privilege of being Jackson's pupils owe to the editor of these volumes a debt of gratitude for this renewal of the inspiration of Jackson's teaching and for the recollections of this most modest and charming of great men which the re-reading of his writings must bring to them.

Lehrbuch der Nervenkrankheiten. Von R. BING. 4te Aufl. S. 570.
Berlin: Urban und Schwarzenberg. 1932. Price 25 M.

The fourth edition of this well-known textbook has been brought up to date and thoroughly revised, but its scope and plan remain unaltered. It is intended for students, and symptoms, therefore, rather than anatomical lesions, determine the arrangement of its subject matter. This has led in places to an unsatisfactory arrangement of the subject; for instance, the dyskinesias, that is all forms of involuntary movement from fibrillation to chorea, paralysis agitans and myotonia, are grouped together in two chapters immediately after those devoted to disease of the peripheral nerves, so that the student meets them before he has learned the more essential features of disorder of the nervous mechanisms concerned in movement.

The pathological aspects of disease are in some instances hardly adequately described or illustrated, and to the student at least the book would have been more useful if more space had been allotted to discussions on the nature and significance of symptoms and signs as evidences of disturbances of functions. The descriptions of the clinical features and of the points on which diagnosis can be based are excellent. A short bibliography has been provided and there is a useful index.

Anatomie élémentaire des Centres nerveux et du Sympathique. Par P. GILIS. 2me Édition. Paris: Masson et Cie. 1932. Pp. 234.
Price 24 fr.

The second edition of the late Professor Gilis' small textbook on the anatomy of the nervous system has been prepared for the press by Dr. Euzière, who has found it necessary to make few alterations.

The book was originally planned as an introduction to the study of the

vegetative nervous system, the importance of which in every branch of medicine has been, in the author's opinion, not fully recognized. But he found that it was not possible to describe properly the sympathetic apart from the rest of the nervous system, and therefore devoted the first half of the book to a study of the anatomy of the central nervous system, or, as he calls it, "the system of relation."

Both sections are concisely written and well illustrated by diagrams; the more usually accepted views are followed, and within its scope there are few statements to which exception can be taken. It is consequently suitable for students and for those who desire acquaintance with an outline of the plan and the chief anatomical details of both nervous systems.

Les Agents physiques dans le Traitement des Maladies nerveuses.

Par H. SCHAEFFER et E. BIANCINI. Paris: Masson et Cie. 1932.

Pp. 187. Price 20 fr.

The former popularity of electricity in the treatment of various nervous disorders has been succeeded, in England at least, by considerable scepticism as to its value, but newer discoveries, more efficient apparatus and other methods of its application present the possibility that in certain cases it may be of therapeutic use. These are discussed shortly in this volume, and though the authors express enthusiasm for some of the results that can be obtained, their attitude is not wholly uncritical.

In addition to the forms of treatment with which all physicians are acquainted, they discuss the value of X-rays in cerebral and pituitary tumours, syringomyelia, the acute stages of poliomyelitis and in other conditions, as well as transcerebral ionization and diathermy, the latter reputed to be useful in some cases of encephalitis lethargica and paralysis agitans. The technique of the various methods of treatment and dosage are adequately described. The use and value of hydrotherapy, massage and other forms of physical treatment are also dealt with.

As the subject matter is arranged mainly under diseases, the book will be a handy guide for those who consult it for practical ends.

Neurofibromatose. Von R. KIENBÖCH und H. RÖSLER. S. 52. Leipzig: G. Thieme. 1932. Price 9.80 m.

With praiseworthy conciseness the authors review the features of neurofibromatosis as revealed in literature and illustrated by their own cases. The points on which most emphasis is laid are the frequency of large intrathoracic tumours of the same structure and origin as neurofibromata in other organs, and changes in bones in Recklinghausen's disease.

Other clinical aspects of the condition and its pathology are adequately discussed too. It is rarely one's fortune nowadays to meet a monograph, in the German language at least, so concisely and lucidly written and so excellently produced.

Les Abscès cérébraux et leur Traitement. Par JEAN PIQUET. Paris: Masson et Cie. 1931. Price 22 fr.

This little volume in the series of "Médecine et Chirurgie Pratique" gives a clear and concise account of the ætiology, pathogenesis, symptomatology and treatment of intracranial abscess. The clinical descriptions given, however, are those of the terminal stages of the condition and will not assist materially to that early diagnosis which is so essential to favourable results from treatment. There is a full table of contents, but no index.

Die juvenile amaurotische Idiotie. Von TORSTEN SJÖGREN. Lund: Berlingska Boktryckeriet. 1931. S. 425. Price kr. 10.

In this monograph the author has collected the extraordinary number of 120 cases of juvenile amaurotic idiocy occurring in 62 Swedish families, 10 of which were inter-related. By tracing many of the families back through six or seven generations, he has been able to study the Mendelian characters of the disease by Weinberg's method and has found it to be transmitted as a mono-hybrid recessive. He found no evidence of hereditary relationship between the juvenile and the infantile forms of the disease, but there was an unusually heavy incidence of epilepsy, imbecility and schizophrenia in earlier generations of affected families. As might be expected from the Mendelian character of the disease, consanguinity of parents was common; in over 25 per cent. of cases the parents had common grandparents or great grandparents. There was also a tendency for the cases to be grouped in certain localities.

Post-mortem material of 9 cases was available, and is to form the basis of a study by Professor Sjövall. Brain puncture was made in a further 9 cases to establish the diagnosis. The author has availed himself to the full of the advantages for the study of the disease which his country offers, and his monograph is a great addition to our knowledge of what appears to be in most countries a rare disease.

Handbuch der Geisteskrankheiten. Herausgegeben von OSWALD BUMKE. Band 8. Spez. Teil IV. Mit 70 Abbildungen. S. 751. Berlin: Springer. 1930. Price 76 Rm.

In this large and very detailed volume of Bumke's "System of Psychiatry" the syphilitic, arteriosclerotic, senile and epileptic disorders are described with thoroughness.

Professor Hauptmann deals with the ætiology and pathogenesis in syphilitic psychoses, showing how much is still obscure in this field. Wilmann's views as to the relation between intensive early anti-syphilitic treatment and the incidence of G.P.I. are discussed fully. The lengthy monographs on luetic psychoses and general paralysis which follow are by Bostroem. After pointing out the relative infrequency of mental disorder due to cerebral syphilis, he deals with the tabetic psychoses (which he repudiates), syphilitic epilepsy and

dementia, as either a residual or a chronic progressive manifestation of the disease; he gives a valuable account of luetic psychoses which appear as schizophrenic, affective and other endogenous reactions. A full description of the clinical features and the diagnosis of G.P.I. occupies more than a fifth of the whole volume; with the succeeding chapter by Plaut and Kihn on the treatment of these conditions it constitutes the most complete available exposition of G.P.I. and the other syphilitic psychoses. The treatment by infection with malaria is reviewed, and such other methods as inoculation with relapsing fever and sodoku, use of specific drugs, proteins and vaccines are appraised.

Stern's section on arteriosclerotic psychoses shows how intimately neurological and psychiatric data are intermingled in these disorders, as also in the involuntal psychoses, which are described by W. Runge. The depressive and paranoid states of the climacteric are a classic battlefield in psychiatric nosology and pathology, but the presentation here is in conformity with modern usage which sees in these conditions a varying complex of other types of reaction. In the chapter on senile psychoses Pick's disease and Alzheimer's disease are also described. The volume concludes with a summary by Grubbe of the present position with regard to epilepsy, in which the problem of epileptoid psychopathy receives special attention. It is doubtful if the author can be followed in his assertion that an operation is always indicated where the attack is chiefly characterized, or regularly ushered in, by definite focal symptoms. In this section, as indeed throughout the volume, the familiarity of each writer with an enormous literature is continually in evidence; the soundness and completeness of the work testify to this and to the authority of the writers in their respective fields.

Methoden der Psychologie des Gefühlslebens. Von GUSTAV STÖRRING.

Abderhalden's Handbuch der biologischen Arbeitsmethoden.

Abt. VI. Teil B., 2 Hälfte. Hefte 2, 3, 4. S. 1125-1646.

Berlin: Urban and Schwarzenberg. 1931. Price Rm. 26.70.

The methods of experimental psychology are being described in the Abderhalden series with the same thoroughness as those dealing with more readily measurable and conclusive data. The present contribution is by Störring. The first part deals with the general theory of feeling. The author points out that introspection, experiment and observation of the abnormal are the chief methods available. It soon becomes clear, however, that the study of morbid psychological phenomena by the analytical method bulks largest in its presentation, so that the greater part of the work might well serve as an account of the psychopathology of affect. Two sections are devoted to various experimental procedures and to data obtained by introspection, but there is no reference to the valuable English work in this field, and the author's quarrel with "Gestalt" psychology narrows the range of the experimental methods recorded. In the second part the methods of investigating the psychology of

judgment in regard to æsthetic and ethical value are discussed; for the latter the ethnological approach is considered valuable, as used by Wundt and Westermarck, while deductive as well as the familiar inductive individual methods are described.

Ergebnisse der Reiztherapie bei progressiver Paralyse. Herausgegeben von K. BONHOEFFER und P. JOSSMAN. Pp. 154. Berlin: S. Karger. 1932. Price M. 14.80.

Wagner-Jauregg's discovery is still recent enough to make competent reports on it a matter of practical importance. The value of the malaria method is now assured, but in its elaboration, combination with other infections or with drugs, its social implications and clinical effects there are still many unsettled points. In this volume over two thousand cases of general paralysis, treated in Berlin between 1922 and 1929, form the material for a wide survey of the results obtained by various methods. A number of writers from different clinics and mental hospitals contribute to the work, their general conclusions being summed up by Jossman. In 40 per cent. of the cases there was improvement, in 23 per cent. practical recovery. In a large number the abnormal serological findings cleared up after pyrexial therapy, without use of anti-syphilitic remedies. The chief adjuncts or substitutes for the familiar malarial treatment were sulfosin, repeated inoculation with malaria and spirochætal vaccines. The paranoid-hallucinatory forms which may follow treatment are discussed, and there are final chapters on the pathology and social aspects of the disease.

L'Evolution psychiatrique. Par plusieurs auteurs. 1931. Paris: Maloine. Pp. 105. Price 16 fr.

The present work is the production of that small circle of French psychopathologists whose troubled history has recently been told by E. Minkowski.

The first paper, by H. Codet, is on "Les Emotifs et les Impressionables." It is refreshing to find a French author who recognizes the artificial nature of any division of anxiety reactions into vagotonic and sympathicotonic; in the vagotonic variety here described depressive features appear to predominate. P. Guiraud's rather rambling report of some cases of murder without apparent motive is followed by an appreciative account by E. Minkowski of the psychiatric work of Maurice Mignard, whose early death was so deplored by the few familiar with his researches into schizophrenia and psychopathology in general. M. Montassut writes on neurasthenic fatigue, regarded as a form of chronic alkalosis, and Sophie Morgenstern gives the conventional psycho-analytic views on the important "depersonalization" syndrome.

Psychopathic Personalities. By EUGEN KAHN. Pp. 521. New Haven: Yale University Press. Humphrey Milford. 1931. Price 22s. 6d.

This book has already been noticed here, when it appeared as a contribution to Bumke's "Handbuch der Psychiatrie." It represents an effort to cope with the difficulties of classifying personality, and especially its morbid variants. The clinical part is sober and detailed. The translation is too often reminiscent of the original German. There is no alphabetical index of subjects.

The Psychology of Men of Genius. By ERNST KRETSCHMER. London: Kegan Paul. 1931. Pp. 256. Price 15s.

This book of Kretschmer's, like most of his writings, is vivid and original rather than convincing. It is well written, but more likely to stimulate the casual reader than to satisfy the specialist. The relation of special endowment to mental disorder is an old question, and from the now urgent standpoint of eugenics a very important one, but it can better be studied by statistical and genealogical methods than by belletristic guesses or unproven assumptions about racial and constitutional attributes. So long as the work is recognized as a brilliant essay and not regarded as typifying the methods of modern psychological study, it may be read with profit.

The Problem of Genius. By W. LANGE-EICHBAUM. Translated by Eden and Cedar Paul. Pp. 187. London: Kegan Paul. 1931. Price 8s. 6d.

This is a well-translated summary of the conclusions reached by Lange-Eichbaum in his larger work "Genie, Irrsin und Ruhm." He points out how mutable a value genius represents, and how necessary it is to recognize its accidental and transitory aspects. Fame, talent, insanity and civilization are the topics in relation to which genius is discussed with a lucidity by no means superficial. Many authorities would question the author's general statement that "nine-tenths of genius is intimately associated with psychopathy or psychosis," but there is much to support his views as to the influence of mental disorder, where present, upon the manifestations of genius.

Körperlich-seelische Zusammenhänge in Gesundheit und Krankheit. Von WALTER H. v. WYSS. Pp. 128. Leipzig: Georg Thieme. 1931.

Dualistic studies of the relation between mind and body are as yet far from satisfying the physiologist or the philosopher. Dr. von Wyss directs his little book to doctors, who are seldom either. The influence of the newer

schools is evident in the theoretical part, but he has avoided the stumbling-block of metaphysics, and wisely contented himself with assembling our available knowledge on the bodily concomitants of mental states, especially as to mood and expression. It is impossible to read this thoughtful and informative contribution to medical psychology without being impressed by the necessity for regarding function and the total integrated person as more important than isolated structures.

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EDITOR.



BRAIN.

PART 2, VOL. 55.

CERTAIN PATHOLOGICAL ASPECTS OF NEUROSYPHILIS.

BY RUBY O. STERN.

(From the Laboratory of the National Hospital, Queen Square, London.)

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INTRODUCTION.

DURING the last two decades earlier recognition of the various forms of neurosyphilis has resulted in much clinical and subsequent pathological study of this manifold disorder. The discovery in 1917 of the beneficial effects of induced malaria in general paralysis has especially stimulated a revival of interest in that malady. Neuropathologists have been particularly active during the last five years in investigating cases of general paralysis which have been treated by malaria, and they have produced exhaustive but conflicting reports both on the histopathology of the brain and on the mode of operation of the treatment.

Little attention has, however, recently been paid to the histopathology of cases of early general paralysis thoroughly treated by means other than malaria. The histological comparison between malarial and non-malarial treated cases rests on the classical descriptions of such

early workers as Nissl, Alzheimer, Achucarro and Mott, who saw only the most severe forms of untreated or inadequately treated cases.

Further, possible differences in the histopathological picture of general paralysis at different periods of life have not hitherto been generally considered. As Critchley has lately shown, the tissues of the brain in the elderly differ both in their minute structure and in their reactions from those of the young subject.

Freeman has remarked on our scanty knowledge of the extra-cerebral pathology of neurosyphilis, particularly of general paralysis, but he himself has made a valuable contribution to it.

The investigation of which this study forms a part was planned along lines suggested by the foregoing brief sketch of a few of the fertile sources of inquiry available to the pathologist in the field of neurosyphilis.

The material at my disposal consisted of thirty-six cases: twenty-eight of general paralysis and tabo-paresis, and eight of tabes dorsalis. Thirty-three of these had been patients in the National Hospital for Diseases of the Nervous System, Queen Square, and I am indebted to members of the honorary staff of this hospital for permission to record them. I have also to thank Dr. Poynton who has kindly allowed me to examine pathologically and quote a case of a child with congenital general paralysis who was under his care at the Hospital for Sick Children, Great Ormond Street; and Dr. G. Griffiths who kindly supplied me with pathological material from, and clinical notes of, two cases at Cheddleton Mental Hospital.

Post-mortem reports have been quoted somewhat fully, as in some cases which came to post-mortem before this investigation was begun in 1928 no microscopic examination of the viscera was made. I am greatly indebted to Dr. J. Godwin Greenfield for allowing me to use his reports on the post-mortem examinations and on the cerebrospinal fluids.

As it would be of little interest to present complete pathological reports of all the cases examined, a few illustrative cases have been recorded. These serve to demonstrate especially the lesions found in mild and severe types of paresis not treated by malaria: those found immediately after or shortly after malarial therapy; and those found in the case of a patient who died during a relapse. A report of the one congenital case has been included for comparison with the case of the oldest patient. Observations, however, have been based on the whole series, not on these particular cases only, and where it has seemed necessary to refer to other cases in order to elucidate a certain point, this has been done.

PATHOLOGICAL REPORTS.

Sections were made in all cases from the precentral and anterior frontal areas of the brain and wherever possible from the basal ganglia, mid-brain and medulla. The spinal cord was examined if the clinical symptoms and signs indicated the presence of a lesion in it, or if evidence of disease other than a slight arachnoiditis was found. A microscopical examination of the viscera, especially of the liver and aorta, was made wherever possible, actually in eleven cases.

The following methods were used on sections of the cerebral cortex from every case: The Prussian-blue method for the demonstration of iron-containing pigment and a method for demonstrating microglia on frozen sections; iron-haematoxylin with van Gieson's counterstain and Nissl's toluidin blue method on celloidin sections. Where material fixed in formol-bromide was available (as it was from 1927 onwards), this was used for Cajal's neuroglial method and for Hortega's microglial method. In lieu of material fixed in formol-bromide, that fixed in formol saline was used for the demonstration of microglia by Cone and Penfield's modification of Hortega's method, which proved satisfactory. Several blocks of the prefrontal and frontal cortex from each case were stained for spirochætes by Jahnke's method, and in two cases sections of blocks from the mid-brain and medulla stained by Jahnke's method were cut, every tenth or fifteenth section being mounted and examined. Control material from a brain containing many spirochætes was stained for comparison at the same time as most of the other sections. Spirochætes in the control material did not once fail to stain by Jahnke's method. Latterly Kanzler's method for the demonstration of spirochætes in single frozen sections was used also, the results being controlled by staining the remainder of the same block of tissue by Jahnke's method. Affected portions of the aorta were stained for spirochætes in all cases in which a definite mesaortitis was present, whether spirochætes had been found in the cerebral cortex or not.

Case 1, illustrating a mild type of paresis with co-existent tabes.

J. M., a married man, aged 55, was admitted to the National Hospital under the care of Dr. Riddoch on October 6, 1927. He complained of loss of memory and difficulty in walking for one year. According to his wife the patient had become languid and easily tired, but had always protested that he was quite well. His speech had become tremulous; sometimes he was unwilling to speak and sometimes he was communicative. He had fallen whilst walking on several occasions, and had had one attack of "shaking" which lasted for only five minutes, during which time he had been dazed.

On examination the patient was found to be drowsy but fairly co-operative. Speech was tremulous and slurring, but there was no tremor of the tongue or hands. The pupils were small and irregular in outline and inactive to light, but they reacted well on convergence. There was a generalized blunting of sensation to pain and the sense of deep pain was lost in the calves. Vibration sense was abolished over the radial styloids and tibial malleoli. The sense of position and passive movement were normal. The legs were very ataxic. The knee-jerks and ankle-jerks were absent and the plantar responses were flexor.

The heart appeared to be within normal limits as regards size and no murmurs were detected. The pulse was regular in rate and rhythm and the radial artery felt healthy. The patient had a stricture of the urethra and this was associated with some infection of the bladder. The report on the cerebro-spinal fluid was: cells, 8 per c.mm.: 40 per cent. large mononuclears, a few large granular cells. Total protein 0.06 per cent. Nonne-Apelt strongly positive, Pandy strongly positive. Lange 344333211. W.R. positive, in fluid 4444, in blood 4444. The patient had two fits with rigors whilst in hospital and died suddenly on October 28, three hours after the second. A post-mortem examination was performed twelve hours after death by Dr. J. G. Greenfield. Over the vertex of the brain the arachnoid ran firmly over the sulci, which were slightly widened. There was great arachnoidal proliferation in the region of the Paccionian granulations. Over the dorsal surface of the spinal cord there was considerable thickening of the arachnoid, especially in the cervical region, where several whitish, thickened patches were seen. In the chest there was considerable early fibrinous adhesion of both lungs to the pleura with congestion of the lower lobes. The heart muscle and valves appeared healthy. The right ventricle and pulmonary artery contained a firm red coagulum about 14 in. long and less than $\frac{1}{2}$ in. thick. The aorta was covered with whitish cushions of syphilitic aortitis. The liver was normal. The spleen and kidneys were congested. The bladder was very thick-walled and the veins under the mucosa were congested. There was very little evidence of recent inflammation.

Microscopical examination.—The aorta showed proliferation of the intima; the vasa vasorum were thickened and slightly infiltrated with small round cells and plasma cells. There was no obvious destruction of the elastic tissue, but some accumulations of lymphocytes were seen between the elastic fibres. No spirochaetes were found in the aorta.

In the brain much iron was present round the cortical vessels and in the processes of many microglial cells. There was an enormous increase in the number of microglial cells. Rod-cells were numerous and were distributed regularly at right angles to the surface. Many transitional forms of microglial cell were also present, particularly in relation to blood-vessels.

The meninges were greatly thickened and were heavily infiltrated, principally with plasma cells, though a few small lymphocytes and endothelial cells were also observed. The cortex contained a very large number of small

thick-walled vessels which in the more superficial layers of the grey matter were practically free from cellular infiltration. In the deeper layers and in the subjacent white matter several vessels were heavily infiltrated by small lymphocytes. Plasma cells were only occasionally seen. In the basal ganglia similar perivascular infiltrations were observed, particularly in the putamen. Rod cells, in the processes of which iron could be demonstrated, were present in large numbers in the putamen and in the caudate nucleus. There were slight degenerative changes in the nerve-cells of the thalamic nuclei. The vessels and nerve-cells in the mid-brain appeared healthy and no perivascular infiltration could be seen in this region.

There was a great loss of nerve-cells in the prefrontal and frontal cortex. Those which remained appeared for the most part healthy, but a few of the larger nerve-cells were undergoing neuronophagia. The cyto-architecture of the cortex was not greatly altered though the various layers were not so easy to distinguish from each other as in a normal cortex.

Spirochaetes were found in one block of tissue from the right frontal region only. They were very few in number, seldom numbering more than one or two in a section. No spirochaetes were seen in the meninges over the areas of the brain examined. No relationship of the spirochaetes to blood-vessels or nerve-cells could be determined, and indeed the number of spirochaetes present was so sparse that any such relationship would have been surprising. The type of spirochaete was the long form, some having as many as twenty spirals. No short or atypical forms were seen. The spirochaetes occurred in the superficial and deep layers of the cortex but none were found in the white matter. Serial sections of the mid-brain and of the floor of the fourth ventricle failed to reveal spirochaetes.

The spinal cord showed intense meningeal infiltration with plasma cells and lymphocytes, and degeneration of the middle root zone in the lumbar and dorsal regions.

Case 2, illustrating a severe type of paresis.

H. P., a male, aged 42, was admitted to the National Hospital under the care of Dr. Collier on August 22, 1924. He was diagnosed in the out-patient department as a typical case of general paralysis, when he one day had a generalized convulsion and was admitted to hospital in status epilepticus. He died two days later without regaining consciousness. His temperature just before death was 108.3° F.

On examination on the day of admission, the right pupil was found to be larger than the left. Neither reacted to light. The knee and ankle jerks were present. The right plantar response was extensor, the left flexor. The heart was not enlarged and no murmurs were heard. The pulse was rapid and remained at about 112 till death. The arteries were thickened. The report on the cerebrospinal fluid was as follows: Cells 25 per c.mm. Total protein 0.05 per cent. Nonne-Apelt positive. Lange 3444444321. W.R. positive, in fluid 4442, in blood 3210.

A post-mortem examination was performed twenty-four hours after death by Dr. J. G. Greenfield. The brain showed some basal meningitis but no apparent wasting of the convolutions. There was some thickening of the pia-arachnoid along the posterior surface of the cord with miliary gummata over the points of emergence of the lowest dorsal and lumbar roots. The lungs were healthy except for one or two small areas of inhalation pneumonia in each lung. The heart was large and flabby; its chambers were all dilated but not hypertrophied. In the aorta a patchy atheroma was present. The liver and kidneys were healthy. The spleen was slightly congested.

Microscopical examination.—The liver appeared normal except for fatty degeneration in a few cells. There were extensive confluent broncho-pneumonic changes in the lungs. In the aorta the intima was thickened; much of the elastic tissue in the media was replaced by fibrous tissue and the vasa vasorum were infiltrated with small lymphocytes.

Small deposits of iron were visible around the vessels in both the grey and the white matter of the brain, although the sections were stained six years after fixation. The microglial cells naturally did not give a strong reaction for iron after such prolonged fixation, and for that reason their processes could not be well demonstrated, but the processes of rod-cells were sufficiently well stained to show that a large number of these cells was present, and that many lay at right angles to the surface of the cortex. Intermediate, atypical forms of microglial cells were also present, particularly in the deeper layers of the cortex. Many atypical forms of astrocytes were also seen in addition to a general increase in the amount of neuroglia. These abnormal forms were well demonstrated by Jakob's anilin-blue, orange G method, the most obvious and frequent abnormality being a swelling of the cell body with shortening of the processes.

Meningeal thickening was very striking over the frontal cortex. In the depths of the sulci large collections of small lymphocytes could be seen; elsewhere in the meninges there was an exudate containing a number of plasma and endothelial cells as well as small lymphocytes. The cortex was very vascular and nearly every vessel was heavily infiltrated. Cellular infiltration was greater in this case than in any other of the series. Every vessel in both grey and white matter of the cortex had a dense perivascular cuff containing chiefly small lymphocytes, though a certain number of plasma cells were also visible around some vessels. It was not uncommon to see the lumen of a vessel almost obliterated by small lymphocytes. There was no formation of miliary gummata. In the putamen, the caudate nucleus and the thalamus perivascular infiltration was remarkable. In these areas the tissues had become highly vascularized, and even the smallest capillaries were ringed by large numbers of cells which extended from the perivascular spaces into the surrounding tissues. Most of these infiltrating cells were plasma cells and many had bi-lobed nuclei; a few plasma cells contained two and even three nuclei. Numerous small lymphocytes also were present. The globus pallidus was singularly free from cellular infiltration. Deposits of iron were found

round even tiny blood-vessels in the putamen and caudate nucleus; little was present round vessels in the thalamus. Finer deposits of iron were visible in the processes of the rod-cells which occurred in large numbers in the putamen and the thalamus. Numerous astrocytes were also visible in these situations; although it was not possible to demonstrate their processes they were identified by their typical nuclei. Many nerve-cells in the thalamic nuclei were degenerate and were surrounded by satellite microglial cells.

A similar type of perivascular infiltration was seen in the mid-brain, pons and medulla, but in sections through the mid-brain the vessels in the region of the oculo-motor nuclei appeared to be more densely "cuffed" than those in other parts of the sections. The cells of the third nerve nucleus were degenerating and one or two had already degenerated so far as to merit the title of "ghost-cells."

The cyto-architecture of the cortex was grossly disturbed. A large number of nerve-cells had disappeared and many of those which remained were being engulfed by satellite cells. It was impossible to distinguish the layers of the cortex.

An occasional spirochæte was found in sections from one block of tissue from the right frontal cortex (six blocks from the right prefrontal and frontal cortex were examined with negative results). The spirochætes showed no predilection for any particular layer of the cortex; they occurred in the superficial and the deep layers but not in the white matter. Seldom more than two or three could be found in a section. I could not find any in the walls of the blood-vessels or in nerve-cells, and no "swarms" or aggregations of spirochætes were observed. The type of spirochætes present was the short one, having about seven spirals and often ending in a terminal bulb or knob. No ring or other atypical forms were seen. A few long spirochætes having about fourteen spirals were present in the sections examined but were very scanty, seldom more than one being seen in two or three sections. The floor of the fourth ventricle with its ependymal granulations was searched in serial section for spirochætes with negative results.

Case 6, illustrating early post-malarial appearances.

S. A., a married man, aged 33, was admitted to the National Hospital on March 29, 1927, under the care of Dr. Stewart. As the patient was unable to give a reliable history the following account of his illness was obtained from his wife: One year previously the patient had become strange in his manner, childish and bad-tempered. He soon became "impossible to live with." He had had transient attacks of weakness on the left side during the past two years.

On examination, the mental condition of the patient was poor, and his memory was bad. His speech was slurring and tremulous and there was a coarse tremor of the tongue and a fine tremor of the outstretched hands. The pupils were eccentric and oval in shape; they reacted poorly to light and on convergence. The patient was deaf on the right side. On elevation of the

palate the uvula was drawn to the right side. The palatal reflex was absent. Power was greater in the right arm than the left, but better in the left leg than the right. Sensation appeared normal. The knee-jerks were present. The ankle-jerks were very brisk. The plantar responses were flexor. The heart was not enlarged and no adventitious sounds were heard.

The patient was inoculated with malarial blood and eight days after the inoculation he had a fit with loss of consciousness. On recovery there was increased weakness and spasticity of the left arm and leg with a doubtful extensor response on the left side. The patient had six rigors in all, four before the fit and two after, and died on June 11, the twelfth day after the inoculation. The report on the cerebrospinal fluid was: Cells 77 per c.mm., 4 per cent. large mononuclears, 1 per cent. polymorphonuclears. Total protein 0.1 per cent. Nonne-Apelt strongly positive, Pandy strongly positive. Lange 2455553321. Wassermann reaction positive, in fluid 4444, in blood 4441.

A post-mortem examination was made by Dr. J. G. Greenfield twelve hours after death. On removal of the brain and spinal cord the frontal lobes appeared much shrunken and the meninges over them were thickened. Miliary gummata were seen over the sulci. The arachnoid over the dorsal surface of the spinal cord was thickened. Both lungs were congested and the right lung was adherent to the pleura. The heart was not enlarged and only a few atheromatous plaques were seen on the aorta. The liver and kidneys were healthy. The spleen was very much enlarged and softened. The pulp contained no parasites in films.

Microscopical examination.—In the aorta there was perivascular infiltration of vasa vasorum with small lymphocytes. Some small collections of lymphocytes were present in the media. No spirochaetes were found.

Brain: Nearly every vessel in the cerebral cortex was heavily ringed by deposits of iron which occurred in large clumps. A little iron was seen in the processes of the microglial cells. (The sections were stained for iron three years after fixation in formol saline and an intense Prussian-blue reaction of the fine granular deposits of iron in the microglial cells could not therefore be expected). An enormous number of rod-cells were present in the cortex. For the most part they ran in parallel rows at right angles to the surface. Rod-cells were especially numerous in the more superficial layers of the cortex: in the deeper layers there were a large number of intermediate forms between the true rod-cell and the normal microglial cell. These forms were particularly evident around blood-vessels. The cerebral meninges were hyperplastic and heavily infiltrated with plasma cells. A few lymphocytes and endothelial cells were also seen in the exudate. But in the depths of the sulci large accumulations of small lymphocytes were present, and in these masses no plasma cells were found. The cortex was extremely vascular; it appeared almost "riddled" with small thinly-walled blood-vessels. The walls of the larger vessels were thickened. The vessels in the more superficial layers of the cortex were only slightly infiltrated, the infiltrating cells being small lymphocytes. In the deeper layers of the grey matter, and more especially in the white matter, the

large vessels were surrounded by many layers of small lymphocytes. Practically no plasma cells were observed in these infiltrations. In the basal ganglia the vessels appeared to be much thickened, and around a few there was slight infiltration with small lymphocytes. This was especially evident in the caudate nucleus, where also there was proliferation of the microglia with rod-cell formation. Very small deposits of iron were seen in the processes of rod-cells and around blood-vessels. There was a definite loss of nerve-cells in the cortex but those which remained appeared healthy. The cortical laminae were easily distinguishable. No spirochaetes were found in this case.

Case 25, illustrating the lesions found two and a half months after malarial treatment.

H. G., a married woman, aged 45, was admitted under the care of Dr. Grainger Stewart, on March 9, 1926. She was unable to give a coherent account of her illness, but the following history was elicited from her husband: Her illness was dated from a "nervous breakdown" two years previously. Speech had been tremulous and difficult for about six months and for the same time the patient had been depressed and irritable. The patient's first husband had died in an asylum of general paralysis. By him she had had three children, who were alive and well, and had had one miscarriage. By her second husband there had been no children and no miscarriages.

On examination the patient was found to be depressed and disorientated in time. Memory and cerebration were poor. Speech was tremulous and a coarse tremor of the tongue was observed. The right pupil was larger than the left. Both reacted poorly to light but well on convergence. There was some blunting of sensation to pain over the "snout" area of the face, but pain sensibility was otherwise normal. Vibration sense was diminished over the tibial malleoli and the ulna. The knee-jerks were brisk; the ankle-jerks were absent. The right plantar response was a doubtful extensor, the left a definite extensor. Nothing abnormal was detected in the cardio-vascular system. The report on the cerebrospinal fluid was: Cells 70 per c.mm. 10 per cent. large mononuclears. Total protein 0.06 per cent. Nonne-Apelt strongly positive. Pandy strongly positive. Lange 4555543321. W.R. positive 4444 in fluid, 4444 in blood. The patient was given tertian malaria intravenously and died nine weeks later of meningitis secondary to bedsores. (The temperature chart is not now obtainable.)

A post-mortem examination was performed twelve hours after death by Dr. J. G. Greenfield. Large gangrenous bedsores were present over the sacrum and right hip. On removal of the brain very much pus, smelling putrid like a bed sore, was present throughout the whole subdural space, even over the vertex of the brain. In contrast to this there was very little subarachnoid pus, but the subarachnoid space was everywhere infiltrated with chronic meningitis. Over the vertex the sulci were widened. The arteries of the base of the brain showed a little atheroma in the form of thickened gelatinous plaques. The chest was normal except for a patchy collapse of the lungs at their bases. There was a small amount of pericardial fluid present. The

heart was healthy. The ascending aorta was normal, but the descending aorta showed numerous gelatinous plaques of atheroma. The liver was pale and firm and apparently the seat of an early monolobular cirrhosis. The spleen was very much enlarged and dark in colour. The Malpighian bodies were evident. The kidneys were healthy. The uterus was large and thick-walled. The ovaries were healthy.

Microscopical examination.—The liver showed advanced fatty degeneration of the liver cells. There was no evidence of cirrhosis.

In the cerebral cortex there were large deposits of iron around the cortical vessels and a little iron was seen in the processes of a few microglial cells (sections stained four years after formalin fixation). A very large amount of protoplasmic neuroglia was present in the cortex. Many vessels were surrounded by astrocytes, the numerous foot plates of which were attached to the vessel walls. The microglia was greatly proliferated. Many rod-cells were present; some were arranged in parallel rows at right angles to the cortex, others were scattered irregularly through the cortex. Many intermediate forms of microglial cells were observed; some had oval nuclei with a few processes, others had elongated nuclei with many processes, but all stages between the typically normal microglial cell and the rod cell could be found. Intermediate forms were particularly evident in the neighbourhood of blood-vessels.

The meningeal changes were those of a purulent meningitis and bore no relation to the syphilitic lesions in the brain. The cortex was very vascular and the walls of the vessels were thickened. There was little infiltration around the vessels in the superficial layers of the cortex, but at the junction of grey and white matter and in the white matter there was a moderate amount of infiltration with small lymphocytes and plasma cells. In the basal ganglia there were large deposits of calcium in the media of the vessels, which were greatly thickened. A few vessels showed perivascular cuffing, chiefly with small lymphocytes. Many rod-cells were present in the putamen and the caudate nucleus and in the thalamus, but no iron could be demonstrated in their processes. Large amounts of iron were present, however, around the vessels in these regions. A few cells in the thalamus were undergoing degenerative changes. The vessels in the medulla were slightly infiltrated with small lymphocytes, but the vessels in the mid-brain seemed unaffected. The nerve-cells in the mid-brain appeared healthy.

There was a gross loss of nerve-cells in the anterior frontal and frontal cortex. Those which remained retained a normal structure, but their distribution was so irregular that the cortical layers merged one into the other and it was impossible to distinguish the different laminæ.

No spirochaetes were found in this case.

Case 28, illustrating the lesions found twenty months after the last malarial inoculation.

E. B., a male, aged 48, was admitted to Oheddleton Mental Hospital in June, 1927, with a history of increasing fabrication for three years and strange behaviour for six months.

On examination his physical condition was fair. He had wild delusions of grandeur. His speech was slurred and his tongue was tremulous. The pupils were equal and gave the Argyll Robertson reaction. The knee-jerks and ankle-jerks were absent and gait was unsteady. The Wassermann reaction was positive in the cerebrospinal fluid and the blood. Malarial inoculations were given on July 7, 1927, September 26, 1927, July 30, 1928, April 9, 1929, May 13, 1929. Parasites were found in the blood in August, 1927, April, 1929, and June, 1929. A course of seven injections of tryparsamide was given from November, 1927, and mercury with potassium iodide was given from July, 1929, onwards. The mental symptoms persisted unaltered, though the physical condition remained good. Death followed a seizure in February, 1931.

At post-mortem an increased amount of fluid was found in the ventricles. The brain was congested and the gyri were flattened. There was some atheroma of the thoracic and abdominal aorta.

Microscopical examination.—Large deposits of iron were found around most cortical vessels and in the processes of the microglial cells. There was an enormous overgrowth of microglia, especially in the superficial layers of the cortex. Only a few typical rod-cells were seen and these did not present an orderly arrangement relative to the surface of the cortex, but many atypical forms of microglial cell were visible, the commonest being an elongated cell with a large number of processes. Many microglial cells were acting as satellites to nerve-cells and appeared to be engulfing them. By prolonging the impregnation with silver in the method used to demonstrate microglia, the processes of the protoplasmic astrocytes were sufficiently well stained to allow of the statement that the protoplasmic neuroglia was greatly increased in amount.

The meninges were hyperplastic and heavily infiltrated and in the depths of the sulci there were large accumulations of small lymphocytes. Elsewhere in the meninges the cells were mainly plasma cells and endothelial cells. The cortex was very vascular and the walls of the cortical vessels were much thickened. Most vessels, especially in the deepest layers of the cortex and in the white matter, were surrounded by wide cuffs of cells of which plasma cells formed a certain proportion, though the majority were small lymphocytes.

Very few nerve-cells remained in the anterior frontal and motor cortex, and most of these were surrounded by satellite cells. The pattern of the cortex was grossly distorted and it was almost impossible to distinguish the separate layers.

Enormous numbers of spirochaetes were present in several blocks of tissue from the prefrontal cortex, but in other blocks from the frontal region not one single spirochaete could be found. Although the typical "swarms" described by Jahnke were not observed, distinct aggregations of 40 to 50 spirochaetes were seen in some parts of sections. The most common arrangement was the diffuse one in which spirochaetes were scattered throughout the section and appeared in all layers of the cortex. A number of spirochaetes were seen in

relation to the cortical vessels, the walls of which contained many, but only once was I able to satisfy myself that a spirochæte lay actually in the lumen of a vessel. Even in sections cut at 3μ it is difficult to be certain that spirochætes are in the lumen of the vessel and are not merely lying above or below the vessel, but in one vessel cut longitudinally the most careful focusing did not reveal any discrepancy between the level of the vessel and that of the spirochætes in its lumen. I could determine no relationship of spirochætes to nerve-cells. The limiting membrane of nerve-cells apparently presents an impenetrable barrier to the spirochætes; for although clusters of spirochætes surrounded nerve-cells in many sections, nowhere could I find a spirochæte inside a nerve-cell or in the process of passing through its wall. Both long and short forms of spirochætes were present, but all forms were typical, i.e., they exhibited regular, even spirals. I did not observe any of the atypical forms which Jahnel has described in the brain and Warthin in the aorta. The spirochætes were limited to the cortical grey matter; none were found in the white matter of the cortex or in the ependymal granulations in the floor of the fourth ventricle, which was the only other part of the brain available for section.

Case 27, illustrating congenital paresis treated by malaria; death ten months after treatment.

E. W., a male child, aged 8 years and 10 months, was admitted to the Hospital for Sick Children, Great Ormond Street, under the care of Dr. Poynton, in February, 1928, with a history of fits and mental deterioration beginning at the age of 6 years. His mother had a very strongly positive Wassermann reaction. On examination the child was abnormally loquacious and of poor mentality. The pupils reacted to light. The knee and ankle jerks were present and the plantar responses were flexor. The report on the cerebrospinal fluid was: Cells 5 per c.mm., all mononuclears; protein, 0.025 per cent; Lange reaction gave a paretic curve; Wassermann reaction strongly positive.

The child was given malarial blood hypodermically on February 11, and the fever was terminated by quinine on March 16. When readmitted for observation on November 26, 1928, no alteration in the mental condition was noted. The knee and ankle jerks were then present. The cerebrospinal fluid contained 5 cells per c.mm., all mononuclears; globulin was greatly reduced in amount; Lange 5555443100; Wassermann reaction positive 4444. The child was then given salvarsanized serum by the cisternal route. After cisternal puncture on December 13, 1928, he passed into status epilepticus and died in coma.

At post-mortem examination the bones of the vault of the skull were found to be very much thickened. There was great congestion of the veins of the scalp. The dura was very adherent to the skull in the region of the longitudinal sinus. The dura and pia-arachnoid were much thickened. The brain was deeply congested. There was very little flattening of the convolutions, but wide dilatation of the lateral ventricles. Granular ependymitis was seen in the floor of the fourth ventricle. The vessels at the base of the brain were

thicker than normal. The spinal cord appeared normal. The thymus was very large and weighed 32 grm. Both lungs were very congested. The heart showed a small patch of atheroma on the mitral valve and another patch near the opening of the right coronary artery. The liver and spleen were both enlarged, and the spleen was adherent to surrounding structures. On section it was soft and diffuent. The kidneys were very congested. The suprarenals and testes appeared normal.

Microscopical examination.—The liver showed fatty degeneration of a few cells and the formation of fine strands of fibrous tissue between the columns of cells. It was greatly congested, all the blood-vessels being widely dilated.

In the brain, a small quantity of iron was seen in the processes of the microglial cells and around blood-vessels. There was a large increase in the number of microglial cells, especially in the neighbourhood of the cortical vessels. A fair number of rod-cells were present, but those did not show any constant arrangement relative to the surface of the cortex. Many abnormal types of microglia cells with indented nuclei were observed. The cerebral meninges were much thickened and a cellular exudate consisting mainly of plasma cells and large lymphocytes was present. The cortex was exceedingly vascular and the walls of many of the vessels were evidently thickened. Only very slight lymphocytic perivascular infiltration was observed around a few vessels; for the most part the vessels were singularly free from infiltrations. There were a few ependymal granulations in the floor of the upper part of the fourth ventricle. The vessels in the vicinity of the ventricle were thickened and surrounded by "cuffs" of cells, mainly lymphocytes.

The nerve-cells in the anterior frontal cortex appeared to be greatly diminished in number but those which remained were normal. Lamination of the cortex was not disturbed.

No spirochætes were found in this case.

HISTOLOGICAL FEATURES OF MALARIAL TREATED AND NON-MALARIAL TREATED CASES OF GENERAL PARALYSIS.

Before discussing the chief points on which various workers differ in their observations on the histology of general paralysis treated by malaria, it appears relevant to consider briefly the outstanding histological features of a typical case untreated by malaria.

The reactions of the tissues of the brain in general paralysis fall into two groups, the ectodermal and the mesodermal. The ectodermal group comprises both degenerative and proliferative changes; degeneration of the nerve-cells and fibres of the cerebral cortex, especially in the frontal region, proliferation of the cortical neuroglia, particularly of the subpial fibrous neuroglia, and of the protoplasmic neuroglia in the grey matter. The mesodermal reactions are those of the wandering cells, of the vessels, and of Hortege's "third element," which he believes to be

mesodermal in origin. The wandering cells manifest their activity by perivascular infiltration of the cortical vessels and by infiltration of the meninges, though neither reaction is specific for general paralysis or for syphilis. The high proportion of plasma cells in the infiltrations, which for a long time was considered pathognomonic of general paralysis, may occur in many other conditions, notably in epidemic encephalitis. The arteries of the cortex may show the changes of endarteritis obliterans, but Jakob holds the view that these changes are not constant. The reactions of the Hortega cells, or microglia, are highly characteristic, and one particular reaction, the storage of an iron-containing pigment, is, in the absence of hæmorrhage and of trypanosomiasis, specific for general paralysis. The formation of large numbers of "Stäbchenzellen," or rod-cells, in general paralysis, was first described by Nissl and Achucarro. Spielmeyer emphasized their characteristic appearance and the fact that they were rarely present in other diseases of the nervous system. Hortega traced their origin to mesodermal elements and related them to the reticulo-endothelial cells which are the "scavenger" cells of the body. It is not surprising, therefore, to find that the rod-cells play an important role in "scavenging" in the nervous system:

The picking up, storage and transport of a pigment containing iron, probably hæmosiderin, is one of the chief functions of the microglia, and the presence of a substance in the rod-cells which gives a Prussian-blue reaction is a diagnostic histological feature in general paralysis. Hayashi, in 1913, was one of the first to observe iron in the rod-cells in general paralysis. Lubarsch, in 1917, described it in the rod-cells and in the adventitial spaces of the blood-vessels in the cortex in over a hundred cases. Spatz and Metz, who have done a great deal of work on the subject of the relation of the microglia to the storage and transport of iron in the nervous system, came to the conclusion that in general paralysis the microglia constitutes the sole means of transport of iron from blood-vessels to the tissues, or *vice versa*. The disturbance in the metabolism of iron which leads to the abnormal storage is as yet undetermined. Spatz and Metz suggested a disproportion between supply and utilization; Proescher and Arkush conjectured that the iron seen in the microglial cells in general paralysis came from the nuclei of disintegrating nerve-cells and, being an abnormal form, was more difficult to remove. This supposition is unlikely, seeing that in conditions where there is great destruction of nerve-cells no iron can be found in the microglia.

Jakob did not venture on an explanation of why iron should be so increased in amount in general paralysis, he merely alluded to its value as a diagnostic feature. Lasarew, and Proescher and Arkush, also stressed the utility of demonstrating iron in the microglial cells as a quick method for the diagnosis of general paralysis. The advantages of this method have not yet been generally recognized in this country. Within half an hour of brain section the diagnosis of general paralysis can be made with certainty in all but a very few cases. The reaction for iron not only gives the iron content of the microglial cells by outlining their presence, but it also shows the general distribution of the microglia.

Jakob found that the iron content of the rod-cells ran parallel with the amount of perivascular infiltration. Where there was much perivascular infiltration and much iron in the adventitial spaces of the vessels, there was also a large amount in the microglia. In cases of stationary paralysis and also in cases which succumbed rapidly, Jakob did not find the typical reaction. Proescher and Arkush, on the other hand, found a large amount of iron present in cases which ran a rapid course. Those cases which died in or just after epileptic seizures gave a specially strong iron reaction.

The question of the iron reaction after malarial treatment may be shortly dealt with here as few observations are recorded. Schultze and Steiner mentioned that the Prussian-blue reaction was scanty, but they gave no details as to the length of time the patient survived the treatment. Wilson found that the iron reaction was stronger in the cortex of patients dying within six weeks of the treatment than in cases not treated by malaria, and he attributed this increase to an increased permeability of the vessels. Thereafter a gradual diminution occurred, in the amount of iron around blood-vessels and in the microglial cells, which Wilson supposed was due to decreased permeability of the vessels.

In my series, the Prussian-blue reaction was performed in twenty-seven out of the twenty-eight cases. Of the four cases not treated by malaria large amounts of iron were present around the cortical vessels in three cases (Cases 1, 2 and 3); none was observed in the fourth (Case 4). In Case 1, there was a very large amount in the microglial cells. In Cases 2 and 3, none could be seen in the microglial cells, but as the sections were stained six and eight years after death respectively, the negative results are of no significance. Case 4 presented an interesting picture of complete failure of mesodermal reaction. No iron could be demonstrated in the microglial cells, only a very few rod-cells were present and there was no perivascular infiltration whatsoever in the

cortex. The loss of nerve-cells was striking, and the case though clinically a typical general paralytic was definitely atypical pathologically. It is of interest that the cerebrospinal fluid of this case did not show a paretic Lange curve.

Of the twenty-three malarial treated cases, all except one (Case 21) showed heavy deposits of iron around the cortical vessels. Three failed to give the iron reaction in the microglial cells, but of these, two (Cases 10 and 13), were examined six and seven years after fixation. The other case (Case 21) showed no iron around the vessels, and was of interest in that in spite of a large increase in the amount of microglia very few rod-cells were present, and no perivascular infiltration was seen in the grey matter of the cortex and only a little in the white matter. The nerve-cells were diminished in number and there was a large increase in the number of protoplasmic astrocytes. Here also there appeared to be a failure of mesodermal reaction in spite of malarial treatment. The clinical picture was that of early general paralysis, cerebral symptoms having been present for only nine weeks. It is noteworthy that in this case also the cerebrospinal fluid did not give a paretic Lange curve. The condition of the blood-vessels and meninges did not warrant a pathological diagnosis of meningo-vascular cerebral syphilis in this case or in Case 4, but it would be equally incorrect to describe these two cases as cases of true general paralysis. The other cases treated by malaria all showed varying amounts of iron in the microglial cells, and I could determine no distinction in the amount present between those cases which succumbed during the very early days following malarial treatment and those which lived for nine weeks, ten months and twenty months respectively. (The last case, No. 28, died immediately following a seizure and had long given clinical evidence that the effects of his five malarial inoculations had been transient). There was no evidence that the amount of iron present in the microglial cells was dependent upon the amount of cellular infiltration. Much iron was often present when the perivascular infiltration was slight, as in Cases 22 and 23.

From the results of my experience with the Prussian-blue reaction in this series of cases, it is possible to express the opinion that the reaction is one on which the pathological diagnosis of general paralysis can be based, given that the material is examined within a reasonable time after formalin fixation (within six months allows of a safe margin for differences in technique).

Records of the histopathology of the brain after malarial treatment

have mounted steadily during the past few years, and reference will be made only to the larger series which have been published, as reports of isolated cases or of a few cases do not usually include the views of the writer on the *modus operandi* of the treatment.

Sträussler and Koskinas, who made a comprehensive report on 38 cases, particularly emphasized the fact that they found a predominance of lymphocytes in the perivascular infiltrations. Two cases which died during the treatment showed miliary gummata. Sträussler and Koskinas concluded that the effect of the malaria is to transform the parenchymatous type of lesion into the granulomatous one characteristic of tertiary syphilis.

Gurewitsch recorded 12 cases, and also found an increase in the number of lymphocytes in the perivascular infiltrations. He considered that after malarial treatment the vascular changes are more characteristic of cerebral syphilis than of general paralysis, except in the basal ganglia, where there remains a predominance of the paretic process. Gurewitsch found the glial nodules described by Dürck in pernicious malaria present in a number of his cases which were treated by tertian malaria. The meningitis, which Gurewitsch observed in many cases, he took to be a malarial lesion. Miliary gummata were found in one case and inflammatory foci in another.

Kirschbaum, who reported 22 cases, considered that in the early febrile stage severe lymphocytic infiltration occurred, but that in patients who died later than a month after treatment the infiltrative reactions diminished and the parenchymatous changes were less severe. He found miliary gummata in two cases.

Lehoczky could not satisfy himself that any exacerbation of the inflammatory process took place during the early stages of malarial treatment. In his cases he described a definite diminution of perivascular infiltration as contrasted with untreated cases.

Wilson, who studied 45 cases in Jakob's laboratory, was of the opinion that there is a definite exacerbation of all the inflammatory processes with an increased production of microglia and a lymphocytic exudate within the first month to six weeks after treatment. If the patient survives this period, diminution in the exudate occurs and there is a gradual disappearance of the newly formed microglia. According to Wilson, the cortex even assumes a more normal lamination. A recrudescence of the paralytic process may occur any time after six months, and in these cases a more focal distribution of the inflammatory reaction was found. Miliary gummata were common in these cases,

and in five cases out of six spirochætes were found. Wilson was able to find spirochætes in only one out of twenty-nine cases dying within six months after treatment. The presence of miliary gummata would appear from these figures to favour the finding of spirochætes. This is contrary to the generally accepted view that spirochætes are very rarely present in the region of gummatous lesions in the brain or in the viscera. Wilson did not put forward a definite hypothesis in regard to the way in which malaria acts, though he suggested that altered permeability of the blood-vessels was in some way responsible. He was of the opinion, however, that the chief effect of malarial therapy was the destruction of most, if not of all, of the spirochætes in the cortex.

Geary, whose contribution to the Mott Memorial Volumes contained his experiences of the effect of malarial treatment on the histopathology of general paralysis, recorded 16 cases. In 10 cases which showed definite diminution of the pathological process, the minimum time which elapsed between treatment and death was three months, the maximum two and a half years. Of 6 cases which showed no improvement pathologically, 4 died within a month of treatment. The pathological improvement consisted mainly in a diminution of the perivascular infiltrations. Spirochætes were found in one case only, a congenital one dying eighteen months after treatment. In those cases which died within a month after treatment a lymphocytic reaction was noticed. Geary mentioned that in many cases perivascular infiltration in the cortex had subsided completely, whilst the vessels in the basal ganglia and mid-brain were still surrounded by many cells.

Ferraro also stressed the fact that the effect of the malarial treatment is on the inflammatory exudate. He reported twenty-nine cases and was the first worker on the subject of malarial treatment to compare the changes which malaria may produce in a normal brain with those changes which occur in the paretic brain after therapeutic malaria. The only lesion which Ferraro considered might be due to malaria in paretic cases was swelling of the endothelial lining of blood-vessels, not a typical syphilitic endarteritis, and acute degenerative changes in a few nerve-cells. He was unable to find Dürck's perivascular glial nodules which Gurewitsch observed in his paretic cases. Ferraro found that there was no aggravation of the paretic process during the early stages of treatment. In any case this would be difficult to substantiate as the intensity of the inflammatory changes varies from case to case, and it is obviously impossible to estimate the intensity of the process before treatment. In his cases the perivascular infiltrations did not become

totally lymphocytic ; where the exudate was greatly reduced the number of plasma cells was proportionately reduced. In many cases dying early in the treatment the infiltrations were very slight. Ferraro could not agree with Strüssler and Koskinas and Gerstmann that the essential feature of the malarial treatment is the transformation of the pathological process into the relatively benign gummatous type. He found inflammatory foci which did not present the appearance of miliary gummata in only two cases and in both of these death occurred too early in the treatment for the foci to have been formed during treatment. Ferraro holds the view that as the malaria kills the spirochætes the inflammatory exudate is absorbed because it is no longer needed. The other mesodermal reaction, that of the microglia, also diminishes in course of time, but the ectodermal processes are practically unaffected and there is no true reconstruction of cortical lamination. Ferraro's findings and conclusions have been given at some length because they accord in the main with my own.

Freeman also relied on the presence or absence of the perivascular exudate as evidence of the activity or quiescence of the parietic process. He also accepted destruction of the spirochætes in the brain as the starting point of pathological improvement, and offered the following suggestions as to the manner in which this destruction might take place : the spirochætes might be destroyed by the high temperature to which they were subjected during the rigors ; the microglial cells might become actively phagocytic and destroy the spirochætes ; or at the height of the fever when the nervous tissues were swollen and oedematous (as Kubie has shown occurs at very high temperatures), the spirochætes might be carried into the subarachnoid space by the current of fluid flowing along the courses of the perivascular channels. The main argument against the last possibility is that spirochætes have very rarely been found in the pia-arachnoid in general paralysis. It is much more probable that the spirochætes are destroyed by heat as good results have been obtained clinically from non-infective thermo-therapy.

In Freeman's opinion there may be actual reconstruction of cortical lamination in favourable cases after treatment, although the number of ganglion cells is reduced. But he also admitted that the process of degeneration of nerve-cells might be arrested at a time when atrophy of the cortex had not progressed to a marked degree. In view of the fact that manifestations of syphilis elsewhere in the body were more pronounced in successfully treated cases, that is, in cases dying more than two months after malarial treatment, without signs of an active

syphilitic process in the nervous system, Freeman came to the conclusion that the treatment did not kill all spirochætes, but merely suppressed their activity in the nervous system. This observation, that the lesions outside the nervous system are more frequent and more severe in cases successfully treated by malaria, has also been made by others. Schultze recorded cases of gummata of the skin of the thigh during remissions following malarial treatment. Wagner v. Jauregg reported cases of syphilitic joint disease, and Kirchbaum observed a case in which a gumma of the palate developed during a remission. Dr. W. J. Adie has kindly permitted me to quote a similar case which was under his care, that of a woman who developed gummatous ulceration and subsequent perforation of the soft palate during a remission following malarial treatment. The disappearance of the spirochætes from the brain appears, therefore, to be associated with an increase of their activity in other parts of the body after a certain time has elapsed. It would be valueless to speculate on the cause of this heightened activity in the absence of further pathological reports on both cerebral and visceral lesions.

Jakob regarded the diminution in perivascular exudate and inhibition of fresh neuroglial proliferation as the signs of pathological improvement in treated cases. He did not consider that any reconstruction of cortical laminæ could take place. Although several years ago Jakob was inclined to the view of Strüssler and Koskinas that the effect of malaria was to substitute a "benign" gummatous process for the "malignant" parenchymatous lesion, lately he has formulated his opinion thus: "Im allgemeinen lässt sich das Gesetz aufstellen, dass wir durch die Infektionsbehandlung häufiger und gesetzmässiger eine benigne Umwandlung des Krankheitsprozesses bewirken, wie sie—seltener—auch spontan in allen ihren Variationen zur Beobachtung kommen kann." ("Normale und pathologische Anatomie und Histologie des Grosshirns," Bd. II, p. 738.)

From my series of twenty-four cases treated by malaria I can confirm Ferraro's statement that there is no constant increase in the amount of perivascular infiltration during the first month after malarial treatment. Not one of the cases showed as much infiltration as the three untreated cases which died in or soon after a seizure. The case which showed most perivascular infiltration in the cortex was No. 28, the patient who had had five malarial inoculations and who died twenty months later immediately after a seizure. Slight perivascular infiltration was the rule, though in two instances it was completely absent, in cases which

succumbed twenty-six and thirty-one days after treatment. My cases differed from those of Freeman in that the perivascular cuffing was greater in his cases in the superficial layers of the cortex; in mine the heavier infiltration was always in the deeper layers of the grey matter and not infrequently, whilst there was little infiltration even in the deeper layers of the grey matter, the vessels in the white matter were heavily infiltrated. This was especially noticeable in Cases 5, 6, 8 and 15. There was very little perivascular infiltration in the cortex of Case 27, a congenital paralytic who died ten months after treatment, and in Case 26, in which death occurred two and a half months after treatment.

The microglial reaction appeared to bear no relation to the length of time the patient survived treatment. The congenital case showed as much as any which succumbed a few weeks after treatment.

Degeneration and loss of nerve-cells was greater in the congenital case and in Cases 4 and 21, in which there was no mesodermal reaction and to which reference has already been made. In general the cases did not exhibit gross disturbances of cortical architecture, and loss of nerve-cells, though usually evident, was not conspicuous.

The lesions in the basal ganglia merit special consideration, as in this country more attention has been focused in recent pathological reports on the cerebral cortex than on lower regions of the brain.

Jakob, whose experience of the pathology of neurosyphilis was unique, found the striatum regularly involved in general paralysis, both in cases treated with and without malaria. The thalamic nuclei usually showed degeneration and varying degrees of gliosis occurred in these ganglia. In his book on "Extra-pyramidal Diseases," Jakob gave his opinion that, in cases of paresis with striking disturbances of movement, the tremors as well as the components of the speech disturbances could be attributed to extension of the pathological process to the basal ganglia. Houlton, who found constant changes in the basal ganglia of four cases, also upheld this view; Kalnin made interesting observations on the distribution of the lesions in the basal ganglia and came to the conclusion that the disease might attack certain parts of the basal ganglia as severely as the cerebral cortex. The putamen was involved in every one of his thirty-five cases, whilst the pallidum escaped in all but four. In a large proportion of cases the cells of the thalamic nuclei were degenerated. Kalnin could not trace any relationship between the degree of tremor and the severity of the lesions in the basal ganglia, but all his cases had tremors during life. Steck studied the question of neuroglial proliferation in the basal ganglia and the distribution of the

lesions. Neuroglial overgrowth was constant in the putamen and caudate nucleus, whereas no proliferation occurred in the globus pallidus. The frequency with which lesions in the basal ganglia have been reported make it improbable that the specific lesions of general paralysis were responsible for the unusual choreiform disturbances which Fischer and Vogt described in their cases. Jakob is probably correct in correlating the regular involvement of the ganglia with the tremor, since we know that lesions in this region, such as those of chronic epidemic encephalitis, paralysis agitans, and Wilson's disease, are associated with involuntary movements and especially with tremor.

In my own series, lesions were present in the basal ganglia in sixteen out of twenty-two cases in which they were examined. I was unable to trace any connection between the severity of the lesions and the existence of tremor during life. Perivascular infiltration and the presence of rod-cells in large numbers were the most constant findings. These were particularly noted in the putamen and in the caudate nucleus. In agreement with Kalnin and Steck, I observed the relative freedom from involvement of the pallidum. Many cases showed neuroglial proliferation, and in several of the more long-standing cases degenerative changes were obvious in the nerve-cells of the thalamic nuclei. In Case 2, a very severe type, there was advanced degeneration of the nerve-cells in the thalamus, in the caudate, and in the nucleus of the oculo-motor nerve in the mid-brain. I was unable to satisfy myself that there was any difference in the severity of the lesions in the basal ganglia between those cases which had been treated by malaria and those which had not.

Perivascular cuffing was observed in the mid-brain, especially in the vicinity of the ventricle, in ten cases out of the nineteen in which it was examined. The exudate was not so intense in any of these cases as it was in the basal ganglia. In the congenital case only the medulla was available for section, but in the region of the fourth ventricle slight perivascular infiltration was present. The character of the infiltrations was predominantly lymphocytic in most cases, both in the basal ganglia and in the mid-brain, though a few plasma cells could be found in practically every case, and in some cases, notably in Case 2, in which they extended beyond the bounds of the perivascular spaces, plasma cells formed the chief constituent of the infiltration. Again, I was unable to determine any difference between malarial and non-malarial treated cases in this respect.

Conclusion.—My observations as regards the effects of malarial

treatment agree with those of Ferraro; destruction of spirochætes constitutes the starting point for the recession of the inflammatory exudate; there is no initial increase in mesodermal reaction, and the ectodermal lesions persist.

THE OCCURRENCE OF SPIROCHÆTES IN CEREBRAL SYPHILITIC LESIONS.

Since 1913, when Noguchi announced his discovery of the *Spirochæta pallida* in the cerebral cortex of general paralytics, numerous workers have devoted much time to the problems of determining the distribution of spirochætes in the brain and their relationship to the tissues. Between 1913 and 1917, the difficulty of finding spirochætes in nervous tissues was further enhanced by the technical difficulty, which Noguchi himself encountered, of differentiating spirochætes from wavy nerve-fibres which also had an affinity for silver salts. Noguchi found spirochætes in roughly 25 per cent. of his cases (200). They were confined to the grey matter of the cortex and occurred in all layers of the cortex except the outer layer. No spirochætes were seen in the meninges or in relationship to blood-vessels or nerve-cells. Foster and Tomaszewski in 1914 reported a series of cases with positive results in 44 per cent.

Marie, Levaditi and Bankowski could find spirochætes in only 10 per cent. of cases by Levaditi's method. These authors found the organisms in close relationship to the walls of the smaller blood-vessels in the cortex. Marcus found spirochætes inside plasma cells in the frontal cortex, though he was unable to detect any in relationship to nerve-cells; one spirochæte was seen in the adventitia of a small capillary.

McIntosh and Fildes, who in 1914 reported the results of their examination for spirochætes in seven cases of general paralysis, first examined pieces of fresh brain by dark-ground illumination, and then fixed and stained the pieces by Noguchi's method. Spirochætes were detected in six cases by dark-ground illumination, but in only three were spirochætes seen on section. The organisms were found only in the grey matter and no relationship of them to blood-vessels or nerve-cells could be determined. One spirochæte was seen in the pia mater over the vertex, a situation of great rarity, as Levaditi and Jahnel have only once found spirochætes there. The cases from which McIntosh and Fildes derived their material were all recent and had shown acute manifestations of the disease before death.

The publication in 1917 of Jahnel's method for demonstrating spirochætes in nervous tissue gave a strong impetus to research on this subject as the method allows of a ready distinction between spirochætes, which stain an intense black, and nerve-fibres, which appear light yellow in colour.

Jahnel himself has fully investigated the question of the occurrence of spirochætes in the nervous system and many of his observations are of great value, especially in relation to the question of the occurrence of spirochætes in certain cases of general paralysis and after malarial treatment. In his article, published in 1918, Jahnel first described the three types of distribution of spirochætes which may be found in the nervous system; the diffuse type in which spirochætes are scattered irregularly through the tissues; the "swarm" type in which aggregations of spirochætes, sometimes large enough to be visible to the naked eye, occur in localized areas; and the vascular type, the rarest, in which the walls of blood-vessels are surrounded and infiltrated with spirochætes. Jahnel was of the opinion that the spirochætes, which may very occasionally be found in the lumina of vessels, reach there after death. Usually only one type of distribution is found in one brain.

Spirochætes are most commonly detected in the grey matter of the anterior part of the frontal lobe, though there is hardly a region of the brain in which their presence has not been recorded. Grant and Kirkland, who examined fifty cases of general paralysis and found spirochætes present in 62·5 per cent., maintained that if spirochætes were not present in sections from the anterior part of the frontal lobes they would certainly not be found in any other part of the brain. They met with spirochætes in the thalamus, the corpora quadrigemina, the cerebellum and the grey matter of the aqueduct of Sylvius, but not in the pia mater. Jahnel also found spirochætes in the basal ganglia, in the neighbourhood of the aqueduct of Sylvius, and in all layers of the cerebellar cortex. Sioli, Dieterle, and Pacheco E. Silva also found them in the cerebellum and in the basal ganglia. Jahnel mentioned the rarity of spirochætes in the mid-brain in the region of the oculo-motor nuclei and discussed their possible relation to the production of the Argyll Robertson pupil, but decided it was not possible to draw any conclusion from their presence. Igesheimer has reported two cases of general paralysis in which he found spirochætes in the optic chiasma and optic tract. Aars, in a careful study of thirteen cases of general paralysis and three cases of cerebral syphilis, was unable to detect spirochætes in the meninges, pons, cerebellum or medulla, although they were found in the cerebral cortex in nine cases.

Many more examples might be cited, but sufficient evidence has been given to substantiate the statement that spirochætes may be found anywhere in the brain. Failure to find them either in their most usual habitat or in less common situations, depends not so much on faulty technique or lack of 'patience on the part of the observer as on selection of the wrong type of case.

The experience of most workers has been that the cases in which spirochætes are likely to be present are those which presented the features of euphoria and grandiose delusions during life. Jahnel, Hauptmann, Sioli, Smyth, Aars, all agree on this point.

The cases which have died either in or just after a seizure have provoked a good deal of discussion. Some authors, Jakob and Jahnel for example, maintain that in these cases the death of the patient is due to a liberation of the toxins from innumerable spirochætes which have suddenly invaded the cerebral tissues, and that spirochætes should therefore be readily found in large numbers; others, as Hauptmann and Ehrlich, consider that the fatal convulsive attack is analogous to anaphylactic shock, and is due to the rapid absorption of toxins produced in the process of destruction of many spirochætes by antibodies. Therefore spirochætes would be few or absent in such cases.

Jahnel agrees that if life is prolonged for a few days after such an attack the antibodies called out may have time to destroy the spirochætes, and so none may be found in the brain, but he claims that the presence of the spirochætes and not the reaction against them provokes the convulsive attacks. Grant and Kirkland found spirochætes present in only 21 per cent. of cases in which seizures had occurred, whilst 50 per cent. of their negative cases had died in seizures. Wilson found spirochætes in one case out of six which died in acute attacks.

My own cases, though of interest, are not sufficient in number to allow of any expression of opinion on this point. Of the twenty-eight cases which I examined for spirochætes, twenty-four had been treated by malaria, and only one of these had survived longer than two months. The disappearance of spirochætes from the brain for several months after malarial therapy has been stressed by many. Wilson found spirochætes present in cases which died fourteen days after treatment, and then only in cases which succumbed at a later date than six months from the malarial inoculation. In Geary's series of sixteen cases treated with malaria, spirochætes were found only in one case of juvenile general paralysis which died eighteen months after treatment. Kirchbaum, Schilling, Bratz and Bielschowsky, Jossman and Steenaerts, all reported failure to find spirochætes in cases treated by malaria.

It was not surprising, therefore, that I was able to find spirochætes in only two of the cases which had been treated by malaria. One of these (Case 13) died sixteen days after the inoculation—after having had five rigors. The patient did not die during a rigor. A very few spirochætes were present in the deeper layers of the frontal cortex and those were short forms with bulbous ends and obviously degenerate. Seldom more than two or three could be demonstrated in a section. None could be found in the mid-brain or floor of the fourth ventricle.

The other case (Case 28) was a striking contrast to the last. Malarial inoculations had been given on five separate occasions, the last occasion two years before death. Intensive tryparsamide and mercurial treatment had been given until two months before death, which followed a seizure. Enormous numbers of spirochætes were present in all layers of the frontal cortex, though the numbers varied in blocks of tissue. (The pieces of brain were sent to me already cut into small pieces, and it was not possible therefore to identify the exact region of the frontal cortex with which I was dealing). Although in many sections only a diffuse arrangement could be determined, in a few definite aggregations of forty to fifty spirochætes were seen. These aggregations were hardly worthy of the term "swarm" as the spirochætes were not packed closely together, though they were sufficiently localized to form aggregations. Many spirochætes were also observed in the walls of blood-vessels and one was found lying in the lumen of a vessel. Thus in one brain there were the three types of distribution, which is, according to Jahnelt, a most uncommon occurrence. Hauptmann holds the view that the types of distribution of spirochætes are transitory and are constantly changing; any one, or all three types, may therefore be encountered in the same brain. The findings in this case certainly suggest that this view is correct. I was unable to find spirochætes in the ependymal granulations in the floor of the fourth ventricle. (The medulla was the only other part of the brain available for section.)

The only other positive cases were two which had not been treated by malaria. Both of these died after seizures; one (Case 1) three hours after the seizure, the other (Case 2) two days later. In both these cases spirochætes were extremely scanty. Six blocks of tissue from the frontal cortex were searched without success in Case 2; in the seventh block four sections were obtained which each contained two or three spirochætes. Most of those present were of the short type and showed early degenerative changes, as the formation of bulbous ends, though a few long forms were seen.

I could not find any atypical "rolled up" or ring-like forms such as Jahnke has described in any of my cases. In Case 1, which succumbed three hours after a seizure, the spirochætes were of the long type and none had bulbous ends. The mid-brain and medulla were searched for spirochætes without success in this case.

Of the other two cases not treated by malaria, one died after a seizure, but in neither could I find spirochætes.

My results, therefore, conform to those obtained by most workers in that in at least 50 per cent. of cases not treated by malaria spirochætes can be found, whilst it is extremely difficult to find them in treated cases within six months from the date of treatment; my results, two positive out of twenty-four, give a percentage of 8·4.

With the exception of Sioli, who found a rolled-up spirochæte in a cell infiltrating a blood-vessel, and Marcus, who found one inside a plasma cell, observers have been practically unanimous that spirochætes in the brain do not penetrate either nerve-cells or infiltrating cells; nor do they occur in the subcortical white matter. My observations agree that the nerve-cells and mesodermal cells apparently form impenetrable barriers to the passage of the spirochæte, as I was unable to find any intracellular spirochætes, nor could I demonstrate any in the white matter. My failure to find them in any other part of the brain except the frontal cortex is difficult to explain, as control material was nearly always prepared at the same time and likely parts of the brain (mainly mid-brain and floor of fourth ventricle) were chosen for section.

EXTRACEREBRAL PATHOLOGY OF NEUROSYPHILIS.

The association of syphilitic aortitis with neurosyphilis has long been known clinically, and it is found pathologically in a very large percentage of cases. The possible significance of this association will be discussed later, but it is essential to point out that although syphilitic lesions co-exist in the aorta and in the nervous system, mild degrees of syphilitic aortitis are an exceedingly common finding in cases in which no other syphilitic lesion can be detected. McIntosh and Fildes discovered a definite mesaortitis in a very high proportion of cases at 314 post-mortems taken at random, this in many cases being the sole demonstrable syphilitic lesion. The aorta would, therefore, appear to be the favourite habitat of the *Spirochæta pallida*.

The clinical evidence of the association of aortic and nervous syphilis is much less frequent than is the pathological. Schlesinger, who commented upon the lack of symptoms which many patients with aortic

and nervous syphilis present, found clinically aortitis in 19.2 per cent. of his cases. He stressed the relatively benign character of aortic disease when associated with syphilis of the nervous system, the absence of cardiac pain being a special feature. Schlesinger suggested that destruction of the nerves in the peri-adventitial nerve plexuses might account for the absence of this most characteristic feature of aortic disease, but this suggestion cannot be accepted because, before destruction of nervous tissue occurs, signs of irritation would appear and pain would, therefore, be a prominent early feature. The observations of Schlesinger were not confirmed by those of Carey Coombs, who found that cardiac pain was present in over half his cases of cardiac and aortic syphilis. He found evidence of syphilis of the nervous system in about 18 per cent. of these cases, 10 per cent. showing the clinical manifestations of tabes dorsalis, and 3 per cent. those of general paralysis. Deneke detected clinical evidence of mesaortitis in 40 per cent. of patients with general paralysis, whilst Frisch was able to demonstrate the aortic condition in only 29 per cent. of cases of this disease.

On the pathological side, Straub found aortic disease in 80 per cent. of cases of general paralysis and Daniels and Arndt in 75 per cent. Jakob, in a series of 890 general paralytics, found aortic lesions present macroscopically in 60 per cent. of cases; but a definite macroscopic syphilitic mesoaortitis only in 40 per cent. Microscopically, however, 70 per cent. of aortas from cases of general paralysis were proved to have the typical lesions of syphilitic aortitis. Jakob referred to the two types of lesion in the aorta which Benda described, one showing miliary gummata in the media with areas of necrosis and giant-cell formation, and the more common type in which infiltration with plasma cells and lymphocytes occurs in the media and adventitia, especially in relation to the vasa vasorum. Jakob came to the conclusion that the gummatous type was exceeding rare as he encountered it very seldom in his series of cases.

Freeman did not give exact figures for the proportion of aortitis to general paralysis which he found in his series of 71 cases, but out of 23 cases which died within two months of malarial treatment, 10 had a definite macroscopic aortitis and 6 had syphilitic changes in the myocardium.

The demonstration of the *S. pallida* in sections from aortas with evidence of gross macroscopic syphilitic mesaortitis is simple in cases in which this lesion has resulted in the death of the patient. Warthin, to whom we owe so much of our practical knowledge con-

cerning the presence of the spirochæte in the viscera, has described both typical and atypical spirochætes in a very high percentage of such cases. But in cases in which a concomitant lesion in the nervous system has been the cause of death spirochætes have only rarely been demonstrated in the aorta. Jahnelt found them once, in a case of general paralysis. Grant and Kirkland found them twice in cases of general paralysis; in one case, which had been treated by malaria, no spirochætes were found in the brain, in the other spirochætes were present in the cortex and medulla of the suprarenals as well as in the cerebral cortex. As far as I have been able to ascertain, spirochætes have not yet been demonstrated in the aorta in tabes. Jahnelt in discussing the question of their occurrence in the aorta in general paralysis emphasized the fact that in his opinion although ring-like, "rolled-up" or other grossly atypical forms might be present in the aorta it was wise to accept these appearances as true spirochætes only if typical spiral forms could also be seen.

Syphilitic lesions of organs other than the aorta would appear to be rare in general paralysis and tabes. In his series of 890 cases of general paralysis, Jakob observed cirrhosis of the liver only once, and was unable to satisfy himself that lesions which occurred in other organs were definitely syphilitic.

Freeman, on the other hand, found a high proportion of cases of cirrhosis of the liver in his series of seventy-one general paralytics; thirteen of these had definite cirrhotic changes, a percentage of 18. Freeman remarked that the cirrhotic lesions were more pronounced in cases which had been successfully treated by malaria than in those in which the inoculations had failed, but he could not attribute the cirrhosis to possible harmful effects of the malaria as the disease in the liver was invariably of long standing. It is difficult indeed to explain the wide differences between the findings of Jakob and of Freeman. The possibility of a national susceptibility to visceral syphilis must be considered, especially in the light of Warthin's work on latent syphilis. Comparison with German figures of the frequency of latent syphilitic lesions of the viscera would prove instructive.

In my series of 28 cases of general paralysis, the aorta was examined macroscopically in 23 and microscopically in 11 cases, but in three cases in which no microscopic examination was made the naked-eye appearance of the aorta was typical of syphilitic aortitis. Microscopically all except one case showed definite cellular infiltration of the vasa vasorum and of the media with small lymphocytes and plasma cells, the

characteristic picture of syphilitic aortitis. Thus aortitis was present in 13 cases out of 23, or in 56·5 per cent. This proportion would have been considerably higher if all the aortas had been examined microscopically, for only 5 of the 11 which were sectioned had shown the naked-eye appearances of syphilitic aortitis; the others had shown varying degrees of atheroma, not obviously of a syphilitic nature. Clinical signs of aortic disease had been found in four cases (16 per cent.) of 25 in which a note was made on the condition of the cardiovascular system. Only one of the six tabetic cases, or 16·6 per cent., gave clinical evidence of aortic disease.

The aorta was examined macroscopically in six cases of pure tabes and in two of those there was a definite aortitis. All the others showed moderate to severe degrees of atheroma. Unfortunately only one of those was available for section and in this case the lesions were microscopically typical of syphilitic aortitis. The proportion of cases of tabes in which a syphilitic lesion could be demonstrated was therefore 50 per cent.

All the aortas sectioned were stained for spirochætes, many by Jahnke's method as well as by Levaditi's, but I was unable to detect spirochætes in any one of them.

The rarity with which spirochætes have been found in the aorta in lesions associated with nervous syphilis suggests that it is not the presence of the spirochæte itself, but that of its toxins, which is responsible for the lesions both in the aorta and in the nervous system. In a study on the histopathology of the tabes, I tentatively put forward the suggestion that the aorta might be a focus harbouring spirochætes which could exert their toxic effects on the cord and produce degeneration of the posterior columns in the same way that this degeneration may be produced by bacterial toxins passing along the afferent nerves by the perineural lymphatics. Since that study was written, Carey Coombs in his Lumleian Lectures has expressed the view that the lesions in syphilitic aortitis are due to toxins from the spirochætes which lie outside the aorta, in the mediastinal lymph glands, whence they are able to pour their toxins into lymphatic channels and can thus affect both the aorta and the spinal cords. This hypothesis accords with the parallelism between aortic syphilis and parenchymatous spinal syphilis which Carey Coombs described, and is one which requires to be fully investigated.

I could find no syphilitic lesions in other viscera except in one case, that of a congenital general paralytic, in which there was microscopically an early monolobular cirrhosis of the liver. In two other cases at post-

mortem examination the liver appeared to present the features of an early cirrhosis, but on section the only lesion found was an intense fatty degeneration.

THE AGE FACTOR IN THE HISTOPATHOLOGY OF PARENCHYMATOUS CEREBRAL SYPHILIS.

In order to compare the histological lesions of general paralysis in childhood, adult life and old age, Cases 27, 18 and 13 were selected. Case 27 was one of congenital paralysis in a child aged 8 years and 10 months, who survived malarial treatment for ten months; Case 18 was that of an adult, aged 32, whose symptoms began only six months before admission to hospital and who died twenty-four days after malarial inoculation; Case 13 was that of a man of 62, with a history of symptoms for two years, who died sixteen days after inoculation, having had five rigors.

The only conspicuous difference between the three cases was the greater loss of nerve-cells from the cortex of the child. No cells could be seen degenerating but there had obviously been a gross "falling out" of nerve-cells. The vessels in the cortex of the congenital case were relatively much thicker than those in the adult cases.

The case of the elderly man was singularly uninformative since it presented none of the histological features to which Critchley has called attention. The number of microglial cells was certainly larger than in many cases, but typical rod-cells formed a large proportion of the microglia and this form is not associated with senile changes. No Alzheimer's tangles or other evidence of metabolic disturbances of nerve-cells could be observed. Several areas of the cortex were stained by Bielschowsky's method in an endeavour to demonstrate senile plaques, but without success. It was surprising to find that in the brain of an elderly man with a psychosis those plaques were absent; their specificity for senile dementia would appear to be almost absolute. The adult case, No. 18, was in no way remarkable.

On the basis of those three cases it is obviously impossible to base any opinion on differences in tissue reactions in cases of general paralysis at different periods of life. This study is being continued.

GENERAL CONCLUSIONS.

Three discoveries during the last thirty years, those of Wassermann, Ehrlich and Wagner v. Jauregg have resulted in an entirely new conception of syphilis both clinically and pathologically. This is parti-

cularly true of neurosyphilis, which before the days of the Wassermann reaction, organic arsenical compounds and therapeutic malaria was a disease difficult to diagnose and hopeless to treat. The Wassermann reaction made the diagnosis of neurosyphilis simple; the new therapeutic measures not only altered the clinical course of the disease but modified the pathological nature of the disease process.

All pathologists are agreed that whereas before the introduction of organic arsenical compounds tertiary manifestations of syphilis, especially in the nervous system, were common, nowadays the occurrence of a gumma in the brain, spinal cord or viscera is a great rarity. On the other hand the incidence of syphilitic disease of nervous tissue itself has become more frequent, particularly in those patients who have shown few or no secondary symptoms, and who have been actively treated in the early stages of the disease.

It is generally admitted that the strong reaction of the mesodermal tissues which gives rise to the tertiary phenomena is due to a vaccination of the patient in the secondary stage by the dissemination of spirochaetes and their toxins throughout the body. The suggestion has been made, which is probably correct, that if this vaccination does not occur there is a poor reaction of the mesodermal tissues and spirochaetes are enabled to flourish in the brain; they are not walled off by fibrous tissue. If the secondary phenomena are aborted by early active treatment no immunity is produced, and the so-called parenchymatous form of neurosyphilis results. Many affirm that the effect of malaria on the disease process in general paralysis is to transform the reaction of the parenchymatous type of lesion into that of the gummatous tertiary type. Others deny this and state that there is no evidence of a mesodermal reaction. Certain facts seem to suggest a possible interpretation of contradictory results.

The starting point of any healing process must be destruction of spirochaetes. Experimental evidence by Jahnel and Levaditi is in favour of this destruction being caused by the intermittent high temperature to which they are subjected during the malarial paroxysms. Jahnel and Levaditi have both shown that in rabbits inoculated with the *Spirochæta pallida* production of high, and especially intermittent high, temperatures causes a widespread destruction of spirochaetes. It is possible that toxins liberated by the sudden killing off of large numbers of spirochaetes in the brain during the malarial paroxysms may produce some local or general vaccination as in the secondary stage of syphilis and thereby cause a tendency to a gummatous or mesodermal reaction.

The occurrence of the reaction will be determined by two factors; the rate at which immunity develops in the patient, and the survival of spirochaetes in the brain or in the lesions of latent syphilis which Warthin has shown are so frequently present.

There is a certain amount of evidence to support this contention. In large series of cases, including those of Ferraro and my own, a diminution in the inflammatory exudate has been observed in the first two months after malarial treatment. This phase corresponds to the destruction of spirochaetes. The second phase is that of a remission. During the remission immunity develops in the patient. The appearance of tertiary lesions in the skin, joints and viscera during remissions which numerous workers have observed results from this immunity reaction in the same way as gummata in the tertiary stage are consequent upon vaccination in the secondary stage of the disease. Further, Wilson found in cases which relapsed after a definite remission that there were large numbers of miliary gummata in the brain, and spirochaetes in five cases out of six. This formation of gummata in the brain is a special expression of a potentially general mesodermal reaction. The phase of immunity will determine when it occurs. Whether the lesions produced in this way are as amenable to treatment as the tertiary lesions following the secondary stage we have as yet no means of judging. As Monrad-Krohn wrote: "The killing off of no matter how many spirochaetes does not recreate one single neurone that has once been destroyed"; a truism which explains the frequent discrepancy between clinical and pathological improvement in malarial treated cases of general paralysis.

SUMMARY.

(1) A series of cases of general paralysis and tabes dorsalis has been studied with special reference to certain aspects of the pathology.

(2) Cases illustrating mild and severe types of lesion in general paralysis and the modifications found after malarial therapy have been recorded.

(3) The constant presence of lesions in the basal ganglia in general paralysis identical with, and often as severe as, those in the cerebral cortex has been emphasized, and the relationship of these lesions to the characteristic tremor has been discussed.

(4) The histological diagnosis of general paralysis has been considered, and the conclusion has been reached that except for the demonstration of spirochaetes in the brain the most reliable and certainly

the quickest method by which general paralysis can be diagnosed histologically is by means of the Prussian-blue reaction in the microglial cells. This method is valuable because it is applicable to material after prolonged fixation.

(5) The frequent occurrence of syphilitic lesions, which are often symptomless, in the aorta is contrasted with the rarity of other visceral lesions in general paralysis and tabes dorsalis. The extreme difficulty of finding spirochætes in the aorta in the aortitis which occurs in association with these two forms of syphilis of the nervous system strongly suggests that the presence of the spirochæte is not essential for the development of the aortic lesion; the question of the existence of spirochætal toxins is raised.

(6) The influence of age on the morbid process in general paralysis has been discussed. Degeneration and disappearance of nerve-cells appeared to be the feature of the congenital case; no exceptional lesions could be demonstrated in the brains of elderly patients.

(7) The occurrence, distribution and localization of spirochætes in the brain in general paralysis have been considered, especially in relation to malarial therapy and its mode of action.

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BIBLIOGRAPHY.

- [1] AARS, C. J. "Paralytic Dementia: Localization of *Spirochæta pallida* in the Brain," *Arch. of Neurol. and Psychiatr.*, 1930, **23**, 512.
- [2] ACHUCARRO in *Nissl-Alzheimer's Arbeiten*, 1909, 3.
- [3] ALZHEIMER. "Histologischen Studien zur Differentialdiagnose der Progressiven Paralyse," *ibid.*, 1904, 1.
- [4] COOMBS, CAREY, F. "Syphilis of the Heart and Great Vessels," Lumsden Lectures, 1930, *Lancet*, 1930, **2**, 227, 281, 338.
- [5] CRITCHLEY, M. "The Neurology of Old Age," Goulstonian Lectures, 1931, *Lancet*, 1931, **1**, 1119, 1221, 1331.
- [6] DANIELS and ARNDT. Quoted by JAKOB.
- [7] DENEKE, T. "Ueber die syphilitische Aortenerkrankung," *Deutsch. med. Woch.*, 1913, **1**, 441.
- [8] DIETERLE, R. "Spirochætosis of the Central Nervous System in General Paralysis," *Amer. Journ. Psychiatr.*, 1927-28, **7**, 547.
- [9] FERRARO, A. "The Pathology of Paresis after Treatment with Malaria," *Arch. Neurol. and Psychiatr.*, 1929, **21**, 69.
- [10] FORSTER, E., and TOMASOZEWSKI, E. "Untersuchungen über die Spirochæte des Paralytikergehirns," *Deutsch. med. Woch.*, 1914, **1**, 694.
- [11] FREEMAN, W. "Malaria Treatment of General Paralysis; Histopathologic Observations in Eleven Cases," *Journ. Amer. Med. Assoc.*, 1927, **88**, 1064.

- [12] *Idem.* "Malaria Treatment of Paresis; Extracerebral Pathology and its Bearing on the Modus Operandi," *Amer. Journ. Syph.*, 1930, **14**, 326.
- [13] FRISCH, O. "Nervenlues und Aortitis luetica," *Klinisch. Woch.*, 1923, **1**, 1195.
- [14] GEARY, O. "Observations on the Histopathology of General Paralysis treated with Malaria and Relapsing Fever," *Mott Memorial Volume*, 1930, 201.
- [15] GRANT, A. R., and KIRKLAND, H. T. "Spirochaetes in the Brain in General Paralysis," *Journ. Ment. Sci.*, 1927, **73**, 595.
- [16] GUREWITSCH, M. "Zur pathologischen Anatomie der malariebehandelten progressiven Paralyse," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1926, **105**, 814.
- [17] HAUPTMANN, A. "Spirochaeten und Hirnrindengefasse bei Paralyse," *ibid.*, 1920, **57**, 122.
- [18] HAYASHI, M. "Histologische Studien über Eisenreaktion an der paralytischen Grosshirnrinde," *Neurologia (Japan)*, 1918, **12**, Nos. 1 and 2. (Quoted by JAKOB.)
- [19] HOULTON, T. L. "General Paralysis; Histopathology of Basal Ganglia, Corpus Callosum and Dentate Nucleus in Four Cases," *Arch. of Neurol. and Psychiatr.*, 1929, **17**, 214.
- [20] IGESHRIMER, J. "Spirochaetenbefunde an der Sehbahn bei Paralyse," *Deutsch. med. Woch.*, 1921, **47**, 738.
- [21] JAHNEL, F. "Studien über die progressive Paralyse," *Arch. f. Psychiatr.*, 1917, **57**, 382 and 347.
- [22] *Idem.* "Ueber Spirochaetenbefunde in den Stammganglien bei Paralyse," *Monatschr. f. Psychiatr.*, 1917, **42**, 58.
- [23] *Idem.* "Ueber das Vorkommen von Spirochaeten im Kleinhirn bei der progressiven Paralyse," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1917, **36**, 335.
- [24] *Idem.* "Ueber die Lokalisation der Spirochaeten im Gehirn bei der progressiven Paralyse," *Neurol. Centralbl.*, 1917, **36**, 402.
- [25] *Idem.* "Ueber einige Beziehungen der Spirochaeten zu dem paralytischen Krankheitsvorgang," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1917, **42**, 21.
- [26] *Idem.* "Die Spirochaeten im Zentralnervensystem bei der Paralyse," *ibid.*, 1921, **73**, 310.
- [27] *Idem.* "Das Problem der progressiven Paralyse," *ibid.*, 1922, **76**, 166.
- [28] JAKOB, A. "Normale und pathologische Anatomie des Grosshirns," Bd. 2, Leipzig, 1929.
- [29] *Idem.* "Die Extrapyramidalen Erkrankungen." Berlin, 1923.
- [30] JOSSMAN and STERNBERG. "Ueber Malaria Behandlung der progressiven Paralyse," *Zentralbl. f. d. ges. Neurol. u. Psychiatr.*, 1924, **35**, 442.
- [31] KALNIN, E. "Die paralytische Prozess und die Zentren des extrapyramidal-motorischen Systems," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1924, **89**, 810.
- [32] KIRSCHBAUM, W. "Zur Histopathologie der mit Malaria behandelten progressiven Paralyse," *Arch. f. Psychiatr.*, 1925, **73**, 526.
- [33] *Idem.* "Tertiär-luetische Erscheinungen bei progressiver Paralyse, besonders nach Malariabehandlung," *Deutsch. Zeitschr. f. Nervenheilk.*, 1927, **96**, 61.
- [34] LASAREW, W. G. "Ueber Eisen im Gehirn bei progressiver Paralyse," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1928, **112**, 60; and *ibid.*, 1928, **118**, 485.
- [35] LEHOCZKY, T. v. "Beiträge zur einigen anatomischen Problemen der progressiven Paralyse," *Arch. f. Psychiatr.*, 1927, **80**, 435.
- [36] *Idem.* "Zur Frage der Eisenreaktion im Gehirn. Untersuchungen an paralytischen Gehirnen," *ibid.*, 1928, **85**, 229.
- [37] LUBARSCHE, O. "Ueber die Ablagerung eisenhaltigen Pigments im Gehirn und ihre Bedeutung bei der progressiven Paralyse," *ibid.*, 1922-23, **67**, 1.
- [38] MARCUS, H. "Spirochaete pallida in die Plasmazellen bei der Progressiven Paralyse," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1914, **26**, 245.
- [39] MARIE, A., LEVADITI, C., and BANKOWSKI, J. "Le Tréponème dans le cerveau des paralytiques généraux," *Ann. de l'Inst. Pasteur*, 1913, **27**, 577.
- [40] METZ, A., and SPATZ, H. "Die Hortegaszellen und über ihre funktionelle Bedeutung," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1924, **89**, 138.
- [41] *Idem.* "Die Drei Gliazellen und der Eisenstoffwechsel," *ibid.*, 1926, **100**, 428.
- [42] MCINTOSH, J., FILDES, P., HEAD, H., and FEARNSIDES, E. G. "Parasymphilis of the Nervous System," *Brain*, 1913-14, **36**, 1.

- [43] McINTOSH, J., and FEARNSIDES, E. G. "Comparison of the Lesions of Syphilis and Parasyphilis," *ibid.*, 1914, **37**, 141.
- [44] *Idem*. "Demonstration of *Spirochaeta pallida* in Chronic Parenchymatous Encephalitis," *ibid.*, 1914, **37**, 401.
- [45] MOTT, F. W. Article on General Paralysis in the Oxford Medicine, 1921.
- [46] MONRAD KROHN, G. H. "Some Settled and Unsettled Problems in Neurosyphilis," Mott Memorial Volume, 1930, 295.
- [47] NAKAMURA, J. "Ueber Veränderungen in der Gehirnrinde malaria-behandelter Paralytiker und Luetiker," *Abh. a. d. Neurol. Inst. Wien*, 1926, **28**, 197.
- [48] NOGUCHI, H. "Studien über den Nachweis der *Spirochaeta pallida* in Zentralnervensystem bei der progressiven Paralyse und bei Tabes dorsalis," *Munch. med. Woch.*, 1918, 737.
- [49] NOGUCHI, H., and MOORE, J. W. "Demonstration of *Treponema pallidum* in the Brain of General Paresis," *Journ. of Exper. Med.*, 1918, **17**, 232.
- [50] NISSEL. "Der Diagnose der progressiven Paralyse," *Allgem. Zeitschr. f. Psychiatr.*, 1903 **60**, 215.
- [51] PACHECO, E., and SILVA, A. C. "Localisation du *Treponema pallidum* dans le cerveau des Paralytiques généraux," *Rev. Neurol.*, 1926, **33**, 558.
- [52] PROESCHER, F., and ARKUSH, A. "Pathology and Laboratory Diagnosis of Paresis," *Journ. Nerv. and Ment. Dis.*, 1928, **67**, 21.
- [53] SCHILLING, V. "Biologischeklinische Blutstudien über allgemeine Infektionsfragen an der Infimalaria der Paralytiker, besonders über ihre unspezifische Wirksamkeit," *Zeitschr. f. klin. Med.*, 1924, **100**, 742.
- [54] SCHLESINGER, H. "Oligosymptomatische Mesaortitis und zentrale Lues," *Deutsch. Zeitschr. f. Nervenheilk.*, 1931, **117-119**, 585.
- [55] SCHULTZE, F. "Die Malariaabehandlung der Paralyse," *Deutsch. med. Woch.*, 1925, **2**, 1856.
- [56] SIOLI, F. "Die *Spirochaeta pallida* bei der progressiven Paralyse," *Arch. f. Psychiatr.*, 1919, **60**, 401.
- [57] SMYTH, J. F. "Relation of *Spirochaeta pallida* to Pathological Changes of Dementia paralytica," *Journ. Ment. Sci.*, 1928, **74**, 657.
- [58] STECK, H. "Der striäre Symptomenkomplex bei der progressiven Paralyse," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1925, **97**, 424.
- [59] STERN, E. O. "Study of the Histopathology of Tabes dorsalis," *Brain*, 1929, **52**, 295.
- [60] STRAUSSER, E., and KOSKINAS, G. "Weitere Untersuchungen über den Einfluss der Malariaabehandlung der progressiven Paralyse auf den histopathologischen Prozess," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1925, **97**, 176.
- [61] STRAUB. Quoted by JAKOB.
- [62] WAGNER v. JAUREGG. "Die Moderne Therapie der Neurolyues," *Verhandl. d. 38 Kong. d. Deutsch. Ges. f. inn. Med.*, Wiesbaden, 1926. (Quoted by JAKOB)
- [63] WARTHIE, A. S. "Lesions of Latent Syphilis" *Brit. Med. Journ.*, 1929, **2**, 199, 236.
- [64] WARTHIN, A. S., and OLSEN, R. E. "Granular Transformation of *Spirochaeta pallida* in Arctic Focal Lesions," *Amer. Journ. Syph.*, 1930, **14**, 433.
- [65] WILSON, R. B. "Histopathological Changes following Malarial Treatment of General Paralysis," *Brain*, 1928, **51**, 410.

ACUTE PERIVASCULAR MYELINOCCLASIS ("ACUTE DISSEMINATED ENCEPHALOMYELITIS") IN SMALLPOX.

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"The variolous process possesses, in a marked degree, the power to awaken latent predispositions to nervous disease, as well as to independently disorder function and create anatomical alterations in the various nervous structures of the body." (ALDRICH, 1904.)

INTRODUCTION.

THE encephalomyelitis occurring since 1922 as a sequel to vaccination has evoked great interest and much speculation. With a more or less characteristic symptomatology and a highly characteristic histology, to escape observation the disease, though certainly present in the past, cannot ever before have occurred with its recent frequency. Various observers, according to their tendency to broad outlines or to minute classification, have stressed its resemblance, or lack of resemblance, to certain other demyelinating neuropathies of unknown ætiology occurring independently of the exanthemata. All questions of ætiology must take into account the fact that encephalomyelitis of precisely similar type has followed measles, antirabic treatment, &c. Although during the last few years cases suffering from a mild form of smallpox have been relatively numerous, during the present decade only two examples of encephalomyelitis following variola have been described. Our object in this paper is to show that smallpox, probably no less than vaccinia, is a powerful excitant, direct or indirect, of the type of nervous disease to which, when following vaccination, the title "post-vaccinal encephalitis" has been appended.

NOMENCLATURE.

The term "acute disseminated encephalomyelitis," commonly used in reference to these cases, contains nothing to indicate the specific nature of the lesions by which the disease is differentiated from others

to which the same title has been applied. In the absence of definite knowledge of their ætiology, it is by no means certain that the lesions are primarily inflammatory in nature. In all the encephalitides attributable with certainty to a virus, the primary attack is on the grey matter; this is true also of those due to the majority of bacterial and inorganic toxins. Moreover, since the disease under discussion, excited by a rather heterogeneous group of factors including vaccinia, measles and antirabic inoculation, is in essentials always the same, it is clear that we are dealing with a single clinical and pathological entity; this should be recognized by the use of a single comprehensive term embracing all the cases, whatever their exciting cause. We propose, therefore, to use in this paper the term "acute perivascular myelinoclasia" as indicating its essential features, without bias towards one or other theory of its causation. In using the adjective "perivascular," we do not necessarily imply that the causative agent is blood-borne, for the vessel wall contains the Virchow-Robin space, a direct extension of the subarachnoid cavity; zones of demyelination are also found at the periphery of the cord and beneath the ependyma of the lateral ventricles. We propose the term "myelinoclasia" because the constant and essential feature of the malady, and the histological criterion of its existence, is destruction of the myelin sheaths over a zone around the vessels; because damage to the axis-cylinders, though always present in some degree, is relatively less severe; and because inflammatory phenomena, as perivascular infiltration with lymphocytes, &c., vary greatly in intensity from case to case, and may conceivably be excited by the irritating products of myelin degeneration.

LITERATURE AND STATISTICS.

From an early period of the history of the disease, nervous symptoms have been recognized as complicating or following smallpox; early references are those of Clifton (1724), and Freind (1730). Apart from initial convulsions, delirium and mental changes due to the toxæmia of the disease, many affections of the nervous system have been recorded, but it is often difficult to pick out cases which may have been examples of the type described in this paper. Many cases recovered, and in those which succumbed post-mortem examination frequently failed to do more than differentiate purulent from non-purulent affections.

The frequency of nervous complications has been variously stated. MacCombie (1905) stated that in variola the nervous system is more often involved than in any other exanthem; Rundle (1929), on the other hand, has never seen these complications. Schamberg and Kolmer (1928)

observed eight instances of paralysis among about 3,000 cases of smallpox; of which five died and three recovered. The opinion of Aldrich (1904) has been quoted above, and that of Immermann (1902) is similar.

Among the records of 15,000 cases treated in the smallpox hospitals of the Metropolitan Asylums Board between January, 1893, and December, 1927, the writers found one case diagnosed as Landry's paralysis, the onset of which probably preceded the attack of smallpox; the one, recorded in this paper, of myelitis associated with optic neuritis; five of "meningitis"; eleven of "peripheral neuritis"; one of "paraplegia," and two of "paralysis."

Some of the nervous complications recorded in the literature have evidently been secondary or coincident, as the purulent meningitis of Wagner (1872), and the streptococcal meningitis and myelitis of Auché and Hobbs (1894). Damaschino (1871) described a case which was certainly poliomyelitis. The case of Oettinger and Marinesco (1895) might have been an example of the disease here described but for the authors' claim to have demonstrated micrococci in the infiltrating cells and in the nerve cells; other observers, e.g., Turnbull and McIntosh (1926), do not consider this evidence convincing.

The older writers recorded many cases where peculiar disturbances of speech occurred, either alone or combined with dysfunction of muscles supplied by the bulbar nerves, or with a paralytic or ataxic state. The relation of such conditions to disseminated sclerosis was often discussed. Gubler and Laborde (1871), Guttstadt (1872), Wohlrab (1872), Combemale (1892), and Aldrich (1904), described cases where partial or complete loss of speech alone occurred. In many of these symptoms commenced during the early or toxæmic stage of smallpox and disappeared quickly. Westphal (1872) described four cases in which disturbance of speech was associated with ataxia but with no loss of sensation; words were squeezed out with syllables spaced at equal intervals, and great difficulty was encountered in the pronunciation of certain letters. Whipham and Myers (1886) related similar cases of two women who emerged from the toxæmic stage of smallpox with weakness of the limbs, and with an utterance which was at first incoherent but which later assumed a jerky, squeezed-out character, giving the impression of great muscular effort, and which was apparently not associated with paralysis of tongue, throat or larynx. Difficulty in the pronunciation of certain words and letters is recorded in the first case. There were neither sensory nor sphincter disturbances, and intelligence once regained was acute. Whipham and Myers quote seven similar cases from the literature, in addition to those described by Westphal.

Aldrich (1904) published a number of cases of which two may be outlined. In the first, a boy aged 13 was found, on the twelfth day after appearance of the rash, in a stupid condition from which he could not be roused. For four or five days speech was slow and hesitating; aphasia then developed. When speech returned five weeks later it was slow, scanning and thick. When allowed to walk the patient was grossly ataxic. There was a marked change in his disposition. In the second case, delirium on the third day of the rash was followed by loss of sphincter control, loss of speech, difficulty in swallowing and quadriplegia. Speech returned after three weeks, but marked ataxia persisted for three months. Certain points in the history suggest superadded hysterical manifestations. Kleinberger (1913) and Sottas (1892) have described similar cases.

Spiller (1903) examined a woman observed by Schamberg, who during the initial stage of smallpox was stuporose, barely able to articulate, had difficulty in swallowing, and impairment of power in the arms and legs. Almost complete loss of power in the limbs followed, and later a gradual restoration of function. There was pronounced scanning speech.

There is also to be found in the literature a group of cases in which paralysis of the limbs occurred with or without paralysis of the bladder and rectum.

Leroy d'Étiolles (1856) mentions paraplegia during the incubation period of smallpox in a woman, aged 21; sensation was not affected. After the eruption appeared the palsy improved, but death occurred later. No lesions were found in the central nervous system. In another case complete paralysis and loss of sensation in the lower limbs came on when the rash was desiccating. There was paralysis of the bladder and rectum, and later the left arm was involved. No lesions were found in the nervous system.

In a patient recovered from an attack of confluent smallpox, Gubler and Laborde (1871) observed paralysis of the legs, at first complete but gradually improving over a period of three months.

Bernhardt (1871) and Guttstadt (1872) described a man, aged 28, who on the eighth day of smallpox complained of numbness in the right hand and weakness in the limbs. Loss of power in the right arm increased and the legs became paralysed. Incontinence of urine was present. Post-mortem, no lesions were found in the central nervous system.

Westphal (1874) published details of a man, aged 32, who on the

eleventh day of a smallpox rash was incontinent of urine. Next day there was retention of urine with paralysis of the left leg. On the thirteenth day both legs were affected and later incontinence of fæces was present. On the seventeenth day a sacral bed-sore developed; paralysis was complete but sensation was merely diminished. Cystitis and sepsis led to death four weeks after the onset of paralysis. Post-mortem, some softening of the cord with congestion of the grey matter was noted. Microscopically, the blood-vessels were dilated and invested with sheaths of granular corpuscles. Extensive infiltration with similar cells affected chiefly the grey matter; no changes were demonstrated in the nerve cells.

Westphal also described the case of a man, aged 22, who on the fourth day of the eruption could not move his legs and was incontinent of urine. His condition gradually improved but he later died from perityphlitis. Here the lumbar cord was most affected and the grey matter less than the white. There was but little destruction of ganglion cells. Westphal named the condition "disseminated myelitis."

Piessinger (1898) reported the occurrence of acute myelitis as a complication of smallpox. Immermann (1902) stated that the cord is affected more frequently than the brain, and that paraplegia of rapid onset associated often with sphincter paralysis but without sensory loss may follow either mild or severe variola.

Spiller (1903) recorded two cases. During the third week of smallpox a woman, aged 19, developed inability to move her legs, impairment of sensation and incontinence of urine and fæces. Although partial restoration of power in the legs soon occurred, death followed the onset of severe diarrhoea about two months later. Post mortem, no changes were found, but examination was incomplete. In the second case, a man aged 36. lost power in the legs on the eighth day of the rash. Retention, and later incontinence, of urine and fæces was followed by diarrhoea terminating in death. Before death some recovery of power was noted in the legs. In the lumbar region, where lesions implicated chiefly the grey matter, the myelin sheaths had disappeared from the anterior horns while the degree of involvement of the nerve-cells was slight. In the mid-thoracic region both grey and white matter were affected. At the time he considered the case to be one of poliomyelitis, but he has since (1929) accepted it as one belonging to the group under discussion.

In Eichorst's case (1913), weakness of the legs with abolition of tendon and plantar reflexes suddenly developed on the eleventh day of

the rash. There was no loss of sensation. Urinary and faecal incontinence were succeeded by retention of urine. No spread of the paralysis took place, but the man died three days later of urinary sepsis. At autopsy the nervous system appeared normal. Microscopically, however, the whole length of the cord was beset with hæmorrhagic and inflammatory foci most marked in the lumbar region. The white matter was most affected, and in the grey the nerve-cells were fairly well-preserved even when situated in a densely infiltrated zone. Foci of mononuclear cells lay in the nervous tissues in immediate relation to the blood-vessels and pial septa, and a round-cell infiltrate occupied the perivascular spaces. The illustrations suggest the type of lesion present in our own cases.

Of the two recorded instances of this disease occurring coincidentally with the recent outbreak of post-vaccinal encephalitis, McIntosh and Scarff (1923) examined one. McIntosh (1923) described perivascular and extra-adventitial infiltration accompanied by demyelination around the blood-vessels.

The second was that of Troup and Hurst (1930). Here an unvaccinated man, aged 63, developed symptoms of myelitis on the twelfth day of the rash. Death from sepsis took place nearly one month later. The lesions, almost wholly confined to the cord, brain-stem and cerebellum, were such as are described in the present paper, except for those modifications due to their greater age. The writers studied the returns of the Registrar-General for the period 1925-1929 and concluded that in all probability during that time other undiagnosed cases had occurred.

Summary.—Among the nervous complications of variola, therefore, are recorded affections of the nervous system clinically unlike pyogenic infections or proved after death to be non-pyogenic. Disregarding the cases of initial convulsions, &c., due to the toxæmia of the disease, cases of peripheral neuritis, and cases of coincident or secondary infections, two clinical groups remain.

In the first the most prominent feature is a disturbance of speech remarkably similar in all instances. Following complete inability to speak, the power of utterance slowly returned but resulted at first only in unintelligible sounds. Later speech assumed a typical slow, monotonous form in which the words appeared to be "squeezed out" by great muscular effort, with the syllables equally spaced. Improvement was apt to be extremely slow. Most authors were at pains to draw a distinction between this and the typical "scanning" speech of dis-

seminated sclerosis, and also to stress the appearance of great muscular effort accompanying attempts to talk. In most cases these symptoms were evident early in the attack of smallpox as the patient recovered from the mental disturbances of the toxæmic stage. Owing to its favourable course the pathology of the condition remains obscure.

In the second group paralysis of the limbs, with or without sphincter disturbance, was the prominent feature, and a considerable number of the cases proved fatal; they approximated more closely in their symptomatology, in their temporal relation to the appearance of the exanthem and, as far as we can tell, in their histology, to those we describe.

CASE RECORDS.

The following records of eleven patients suffering from acute nervous symptoms in association with smallpox (nine of whom were under the personal observation of one of us—J. P. M.) are recorded here for the first time.¹ From a clinical point of view we divide the cases into two groups, and shall later discuss the relation, if any, existing between those in the second group and the typical examples of acute perivascular myelinocaliasis forming the first group. The latter consists of seven patients: of these four, including a boy with concurrent vaccinia and variola, recovered more or less completely, while three died and were examined pathologically. The second group contains the remaining four patients, and includes one "borderline" or "abortive" case in which the symptoms were vague and transient; one intermediate between this and the definite cases; a patient in whom nervous symptoms predominated at the onset of the toxæmic stage of smallpox, and a case occurring in the year 1899 of an acute nervous disorder in the course of a severe attack of smallpox. This last case proved fatal, but pathological details are lacking.

Group I.

Case 1.—A. P., aged 10, an unvaccinated boy, had suffered previously from measles and whooping-cough. Initial symptoms of smallpox commenced on December 29, 1929. The eruption appeared on January 1, 1930, and on the 6th there was pain in the back and limbs. On 7th the patient was admitted to hospital with a late pustular eruption of modified smallpox, type six (less than a hundred lesions on the face); his temperature was 99.6° F. and his pulse-rate 100.

¹ For permission to publish clinical details of these cases, with the exception of Case 7, we are indebted to Dr. A. F. Cameron, Medical Superintendent of the L.C.C. Smallpox Hospitals.

On the evening of January 8 the boy was drowsy and listless and complained of pain in the back. On the morning of January 9 the child could be roused only with difficulty, and was resentful of interference. Retention of urine with overflow incontinence was present. The left pupil reacted to light, the right one did not. The patient could swallow but took fluids unwillingly. Tendon, plantar and abdominal reflexes could not be elicited. The arms were slightly rigid but could be moved freely; the legs were flaccid and voluntary movement was not possible. Kernig's sign and head retraction were present. The patient resented pin-prick on the right cheek only and appeared to be insensitive to strong compression of either tendo Achillis. Lumbar puncture gave a clear, colourless fluid. Urine, free from abnormal constituents, was obtained by catheterization. On January 10 there was little change. The right pupil now reacted to light. Tache cérébrale was obtained. The optic discs appeared normal. Lumbar puncture yielded a little blood-stained fluid on which the following report was issued.¹ "Cell count, 595 cells per c.mm. A large number of red cells present. Cultures, sterile. No tubercle bacilli found."

On January 11 the child could be roused to open his eyes and mouth more easily but could not be induced to speak. The left pupil was larger than the right; both reacted to light. Slight respiratory stertor was noticed. At night the temperature rose. Breathing became stertorous and at times cyanosis was marked. Head retraction had become evident; trismus was extreme. Lumbar puncture liberated a stream of fluid which was uniformly blood-stained. At midnight the patient was worse and exhibited increased stertor, cyanosis and hyperpyrexia. Slight movements of the face and upper limbs were apparent. Respiration became gradually more shallow, the pulse failed suddenly and death occurred at 3.25 a.m. on January 12.

The father and a sister of this boy developed smallpox after his removal to hospital; each passed through an uncomplicated modified attack of the disease.

Pathology.—Macroscopically the brain and cord showed considerable congestion. With the naked eye it was possible to detect around a few vessels in the white matter of the cerebral hemispheres greyish-pink translucent rings which later were found to coincide with the more extensive zones of perivascular demyelination. The lungs were congested and œdematous.

Microscopically, the lesions are typical of the acute perivascular myelinolysis which follows certain exanthemata and are in all essentials similar to those occurring after vaccination. Perivascular infiltration with large and small lymphocytes, plasmacytoid cells and occasional plasma cells is more marked than usual, and cuffs several cells deep occupy the perivascular spaces in many parts of the brain and cord. This infiltration occurs in conjunction with the extra-adventitial changes mentioned below and also, particularly in the cerebral cortex, independently of such changes.

Extra-adventitial lesions consisting in wider or narrower zones of demye-

¹ For the reports on blood and cerebrospinal fluid we are indebted to Dr. V. D. Allison, L.C.O. Southern Group Laboratories, Hither Green.

lination with cellular accumulation occur around many of the vessels. (Fig. 1.) In these zones there is some outfall of axis-cylinders with degenerative changes in many of those persisting. The infiltrating cells are chiefly microglial, but where perivascular sheathing is intense lymphocytes and occasional plasma cells may be present in the nervous tissue immediately adjacent to the vessel wall. Fatty products of myelin disintegration are scanty, amounting usually to only a few fine Scharlach-staining granules in the microglial phagocytes. In a few areas of the meninges slight mononuclear infiltration is seen.

In some parts of the cortex there is a diffuse proliferation of microglia, mainly in the form of rod-cells; the cells are not nearly so closely packed as in the demyelinated areas of the white matter and their distribution bears a less obvious relation to the local vessels.

These changes are found in many areas of the cortex and white matter of the cerebral hemispheres; other areas are, however, wholly spared. The caudate nucleus is free from lesions and the lenticular nucleus shows only occasional slightly affected vessels. In the claustrum lesions are very marked. In the optic thalamus intense lesions are present immediately under the ependyma of the lateral ventricles. Throughout the brain-stem the areas of damage are for the most part confined to one side, the other half of the cross-section being almost normal. In the cervical cord this unilateral distribution is absolute, but at lower levels both sides of the cord participate in the inflammation. The grey matter is more severely damaged than the white, and while many vessels of the antero-lateral column are affected, only occasional zones of myelin destruction are found in the posterior columns. Changes of similar or less degree, but bilaterally disposed, are seen at all dorsal segments examined. The lumbar cord is more intensely affected; by coalescence of the zones around adjacent vessels the dense cellular infiltrate appears to be uniform over the whole of the grey matter, in which no myelin sheaths can be recognized. The zones of demyelination around the vessels of the white matter are very broad, and both posterior and antero-lateral columns are heavily involved.

Throughout the nervous system the nerve-cells exhibit mild toxic changes in no way related to the proximity of an affected vessel. Usually, even when situated in a densely infiltrated area, they are tolerably well-preserved, though in the cervical cord the anterior horn cells are definitely more damaged on the abnormal side. Contrary to the usual findings in this disease, in the lumbar region definite destruction of nerve-cells has taken place, especially in the anterior horns where necrotic masses with a phantom nucleus or without any apparent nuclear structure occupy the site of many of the large motor cells. Neuronophagia is not observed.

Of the other viscera only the lungs, in which a capillary bronchitis with areas of incipient bronchopneumonia are present, show any definite abnormality.

Case 2.—Q. G., aged 10, an unvaccinated girl, had suffered previously only from measles. On September 18, 1929, she fell ill with headache, backache

and vomiting; a smallpox rash appeared on the 21st. She was admitted to hospital on the 24th with a discrete vesiculo-pustular eruption of modified smallpox, type six. No other abnormality was then noted.

During the night she complained of severe pain "all up the back." Temperature 101° F., pulse 116, respiration 24. Urine was passed normally. On the morning of September 25 the patient had no power in her lower limbs, which lay flaccid in the bed. She still complained of pain in the back. Retention of urine was now present, enemata were not retained. At night the child was drowsy. Fourteen ounces of urine free from abnormal constituents were withdrawn by catheter.

On September 26 the girl would answer questions fairly intelligently, but it was difficult to hold her attention and she relapsed quickly into a drowsy state. Complete flaccid paralysis of both lower extremities was present, with total anæsthesia up to about the level of the twelfth dorsal vertebra; above this both movement and sensation appeared normal. Voluntary contraction of the abdominal muscles could not be elicited. The optic discs appeared normal. Plantar, tendon and abdominal reflexes were absent. Urine and fæces were retained.

On September 27, temperature 98'4° F. The patient was more wakeful. Anæsthesia now extended to the level of the seventh dorsal vertebra. Clear fluid escaped readily on lumbar puncture, of which the child felt nothing; this contained 74 cells per c.mm., all small lymphocytes. No organisms were seen and cultures on blood-agar were sterile.

The fluid also contained: sugar, 64 mgm. per 100 c.c.; chlorides, 684 mgm. per 100 c.c.; and protein, 0'07 per cent. The Nonne-Apelt test was negative.

On September 28 anæsthesia extended to about the level of the nipples, without any sharp line of demarcation.

On September 29 some return of sensation occurred over the trunk and legs, with hyperæsthesia on the abdomen; there was no change in the paralysis. The patient was again drowsy.

On September 30 drowsiness was less marked and the girl complained of pain in the thighs and over the lower abdomen. True urinary incontinence commenced. Lumbar puncture again gave a clear fluid; the insertion of the needle was now appreciated.

On October 1 the patient was incontinent of fæces for the first time. Normal appreciation of pin-prick on the trunk and hyperæsthesia over the legs were noted; thermal sense was very imperfect over the lower half of the body.

On October 2 lumbar puncture was repeated; the fluid contained 27 cells per c.mm., all small lymphocytes; sugar, 62 mgm. per 100 c.c.; chlorides, 725 mgm. per 100 c.c.; and protein, 0'07 per cent. The Nonne-Apelt test and the Wassermann reaction were negative.

By October 3 all signs of drowsiness had disappeared. Pain was again present in the right thigh. There was no hyperæsthesia, but the patient failed to discriminate between painful and other stimuli over the lower half of the body.

By October 5 some power had returned to the trunk muscles; the child could now roll herself over and struggle into a sitting posture.

On October 9, in spite of continued dribbling incontinence, the urine was still free from abnormal constituents; incontinence of faeces persisted. The patient experienced transient pain in the right foot. Cerebrospinal fluid escaped at an apparently normal rate. It contained 9 cells per c.mm., all small lymphocytes; sugar, 62 mgm. per 100 c.c.; chlorides, 713 mgm. per 100 c.c.; and protein, 0.14 per cent. The Nonne-Apelt test was negative.

On October 16 a plantar response, indeterminate in direction, was elicited on the right side.

On October 17 the skin broke over a small area at the summit of the natal cleft.

By October 19 early spasticity, more marked in the right than in the left leg, was apparent, with a definite extensor plantar response on the right side. Pin-pricks were not appreciated as painful on the legs. Sphincter disturbances had not improved.

October 26 the patient was able voluntarily to contract the abdominal muscles, to flex and extend the great toes, and to a limited degree to flex the legs at the hip-joints. While she could discriminate between and accurately localize pin-prick and light touch, differences of temperature were still very imperfectly appreciated, particularly over the lower part of the back and the upper part of the thighs. Plantar stimulation of either sole elicited an extensor response of the corresponding great toe and foot and a flexor response of the limb as a whole.

By October 30 urine was being voided unconsciously in a reflex manner about every two hours; it remained free from any abnormality. The lower limbs were more spastic. Sensation appeared normal.

By November 6 the child, if supported, could stand and make a few steps. Knee and ankle jerks were more marked on the right side. Only the left upper abdominal reflex could be obtained. Adductor and ham-string spasm began to be apparent, and by November 13 there was a strong tendency to flexion, adduction and internal rotation of the legs. On November 16 return of rectal sense was first apparent. On November 27 the patient could stand unsupported. Muscular spasm had diminished. Extensor and crossed flexor plantar responses were obtained. The patient had limited but definite control of bowel and bladder. Progress hereafter was steady; spasticity diminished and power returned in the lower limbs. Bowel and bladder consciousness and control gradually returned to normal.

The patient was discharged from hospital on January 9, 1930. Her mental state was considered normal. In the lower limbs some spasticity was apparent; muscular power was good; knee and ankle jerks were exaggerated; ankle clonus absent; the plantar responses were extensor, with flexor leg response more marked on the right side. Only the left upper abdominal reflex could be obtained.

In March, 1931, the patient was seen by Dr. Bernard Schlesinger, who has

kindly supplied the following notes of her condition. Mentality normal. Knee and ankle jerks markedly increased; abdominal reflexes present; plantar responses extensor. Some spasm of the adductors of the legs again noticeable; plantar flexion of feet developing.

Two brothers and a sister of this patient subsequently developed smallpox; they remained free from nervous symptoms.

Case 3.—A. Y., a boy, aged 8, had suffered previously from chickenpox, measles and pneumonia. A brother was removed to hospital with smallpox on December 26, 1929, and on 28th A. Y. was primarily vaccinated in one insertion; vaccination was successful.

On January 8, 1930, A. Y. was admitted to hospital with a discrete pustular modified smallpox rash (type six), estimated to be at about the sixth day of development. On the outer surface of the left upper arm was one vaccinia pustule surrounded by a normal zone of reaction. The conjunctiva of the right eye was inflamed. The patient was afebrile.

On the morning of January 12 he was allowed up, but a few hours later he was noticed swaying as he walked. He complained only of feeling tired. The temperature, previously subnormal, had risen to 101° F., pulse 98, respiration 22. About noon the boy was drowsy but could be roused to answer questions, although his articulation was slurred. Breathing was stertorous. A right internal strabismus and weakness of the facial muscles on that side were apparent. The abdominal reflexes were absent. No rigidity or paralysis was obvious in the limbs. The right knee-jerk was absent; both ankle-jerks were present. The plantar response was flexor on the right side, extensor on the left. Kernig's sign was absent. No impairment of sensation to pin-prick was apparent. The vaccinia lesion was crusting, with little surrounding tissue reaction and no undue adenitis. On lumbar puncture clear fluid escaped rapidly.

On January 13 the patient was semiconscious; he lay quietly and breathed normally. Squint had disappeared; but facial weakness was still present. Kernig's sign was positive. The abdominal reflexes and ankle-jerks were absent; knee-jerks were present; plantar responses were indefinite. Dribbling of urine was not associated with distension of the bladder. The boy appeared unable to swallow. Clear fluid, the last portion mixed with blood, escaped rapidly on lumbar puncture. It contained 483 red and 542 white cells per c.mm.; a differential count of white cells showed 43 per cent. polymorphs., 53 per cent. small lymphocytes, and 4 per cent. large mononuclears. No organisms were seen and cultures were sterile. The fluid also contained sugar, 60 mgm.; chlorides, 749 mgm. per 100 c.c., and protein, 0.08 per cent. The Nonne-Apelt test was negative.

On January 14, the temperature ranged from 97° F. to 100.2° F. The boy was unconscious. The limbs were flaccid and knee-jerks could not be obtained; Kernig's sign was absent; otherwise the physical signs were unchanged. Catheterization yielded about 12 oz. of acid urine containing a trace of acetone. About 25 c.c. of clear fluid, the last portion tinged with blood, were

obtained by lumbar puncture. Examination showed white cells 345 per c.mm. and numerous red cells, protein 0.09 per cent. The Nonne-Apelt test and the Wassermann reaction were negative. The blood gave a negative Wassermann reaction and contained 41 mgm. per cent. urea.

On January 15 the patient lay unconscious and completely immobile with saliva running from the side of the mouth; 30 c.c. of clear fluid were removed by lumbar puncture and 15 c.c. of human convalescent smallpox serum injected. At night the temperature rose to 102.4° F. On January 16 cyanosis was apparent, salivation was more marked, and spasmodic twitching occurred on the left side of the face. The plantar reflexes were extensor. Retention of urine and faeces persisted and acetonuria was present. Cerebrospinal fluid, slightly hazy from admixture with blood, was withdrawn by lumbar puncture.

On January 17 the temperature became subnormal and the pulse fell to 60. A small crop of herpetiform vesicles was noticed on the parietic side of the mouth. By putting up his hands to the areas stimulated the patient responded to a touch anywhere on the face. A differential count of white cells present in the cerebrospinal fluid showed: 22 per cent. polymorphs., 74 per cent. small lymphocytes, and 4 per cent. large mononuclears. The fluid contained 0.10 per cent. protein, and the Nonne-Apelt test was negative.

On January 18 purposeful movement of limbs was noted and milk was swallowed from a spoon; pin-prick seemed to be appreciated generally. Lumbar puncture was repeated. At night the patient was incontinent of urine. On January 19 the boy was again deeply unconscious. Intermittent incontinence of urine (containing a cloud of albumin) became established. At night the patient sometimes answered when addressed. Marked sweating of the head was apparent. Cerebrospinal fluid was clear and escaped readily on lumbar puncture.

On January 21 the cerebrospinal fluid appeared to be under greater pressure. The patient was brighter and answered questions readily. The plantar responses were flexor; the left knee-jerk only was obtained. Frequent nose-rubbing was now evident for some days. On January 22 both ankle-jerks and the left knee-jerk were elicited. Faeces were retained; incontinence of urine continued. Lumbar puncture was repeated.

On January 25 facial weakness was less obvious and the patient had regained some control over micturition: the urine still contained some albumin. Abdominal reflexes and knee-jerks could not be obtained; ankle-jerks were present.

On January 27 the patient was mentally alert. No difficulty in deglutition, mastication or articulation was evident and nasal feeding was discontinued.

By February 2 the boy could sit up in bed and read. The urine was free from abnormal constituents. Micturition and defaecation were normal. The abdominal reflexes were still unobtainable, but ankle-jerks, knee-jerks and flexor plantar responses were present. After return to consciousness masturbation was a troublesome feature.

On February 4 the patient sat up in a chair and a few days later commenced walking exercises. Rapid progress was made and general bodily wasting soon disappeared.

On February 27 the patient was discharged from hospital. The general condition was good and the mental state appeared normal. The boy presented some monotony of expression, but according to his parents this had always been so. Speech was slow but not scanning and articulation was normal. There was no paralysis. Knee and ankle jerks were present; the plantar responses were flexor; the abdominal reflexes were still wanting. Four months later the boy's mother wrote to say that he was leading a normal life at school.

H. Y., an unvaccinated brother of this patient, was removed to hospital on December 26 and passed through an uncomplicated attack of smallpox. Two other brothers, J. Y. and R. Y., were successfully vaccinated on December 28 and 30 respectively; both developed smallpox which ran an uncomplicated course. It is worthy of note that J. Y. was vaccinated on the same day as A. Y., possibly with the same batch of lymph.

The onset of nervous symptoms in the case of A. Y. occurred on the sixteenth day of successful primary vaccination and about the ninth day of a smallpox rash. The incubation period is within the limits attained by cases of acute perivascular myelinoclasia following either vaccinia or variola, but more closely approximates to the mean average of those associated with the latter disease.

Case 4.—H. R., an unvaccinated man aged 21, had in childhood suffered from measles and pneumonia. His present illness commenced insidiously. A smallpox rash appeared on January 6, 1930, and on 10th the man was admitted to hospital with a discrete pustular eruption of modified smallpox (type six). On 12th he was allowed up.

On the morning of February 18 he felt giddy and sleepy and had to be assisted back to bed. The temperature was not raised. In replying to questions the speech was slow. During the night he was incontinent of urine.

On February 19, temperature 99.2° F., pulse 92, respiration 20. The man complained of headache and pain in the legs, and was dull and confused. Some cervical rigidity was present. The pupils were small, equal, and reacted to light. Kernig's sign was absent; knee and ankle jerks and abdominal reflexes were not obtained; plantar responses were flexor. At night the man was semi-conscious but could be persuaded to answer questions. Pain in head and legs had ceased. Retention of urine was relieved by the catheter; the urine was normal. Faeces were retained. Weakness of the right face was noted; otherwise the cranial nerves were normal, as were the upper extremities. In the lower limbs, however, very little power existed. The patient could just move his toes and feet. Voluntary muscular contraction in the legs was perceptible, but limited and ineffectual. Both legs were flaccid; the knee and ankle jerks were wanting; the plantar responses were flexor. Abdominal reflexes were absent. No sensory loss was detected.

On the morning of February 20, temperature 100.6° F., pulse 86, res-

piration 20. Large bullæ had appeared on the dorsum of the left foot, on the extensor surface of the left great toe, and over the left hip. The patient was conscious, but drowsy and dull. Clear fluid escaped readily on lumbar puncture. This contained 470 cells per c.mm., of which 358 were red and 112 white, 1 per cent. polymorphs, 96 per cent. small lymphocytes, and 3 per cent. large mononuclears. Cultures were sterile, and no organisms were seen. The fluid also contained sugar, 80 mgm. per cent.; chlorides, 743 mgm. per cent.; and protein, 0.10 per cent. The Nonne-Apelt test and the Wassermann reaction were negative; blood contained 64 mgm. urea per cent.

At night the patient was more stuporose and mostly lay immobile, but at times ground his teeth. The pupils were small and barely reacted to light; an intermittent right external strabismus was evident. The plantar responses were not obtainable. Pin-prick on the face, arms and hands elicited movements of resentment; elsewhere it was apparently not appreciated.

On February 21, at times the man appeared to be fully conscious. Squint was no longer evident. Weakness was now noted in the arms, more especially in the right; pin-prick was appreciated above the level of the nipples. A flexor plantar reflex was obtained on the left side. Clear fluid under great pressure was withdrawn by lumbar puncture, and 10 c.c. human convalescent smallpox serum injected intrathecally. At night teeth-grinding and twitching of the left face occurred.

On February 22 the man was mentally clearer and more able to keep awake. He could move his head from side to side, but was unable to raise it from the pillow. Weakness was more marked in the right than in the left arm; no voluntary contraction of the muscles of the abdominal wall could be made out. The lower limbs were flaccid and powerless; the condition of their reflexes was unchanged. Pin-prick was appreciated as a blunt sensation over feet and ankles; above this anæsthesia was complete to the nipple level, after which pin-prick seemed sharp and painful. Shooting pains were felt in the arms. About this time priapism commenced to be a troublesome feature.

On February 23 the patient complained of pain in the neck, which was stiff but not retracted. Lumbar puncture was repeated, and for the first time the man experienced pain during it.

On February 24 the patient slept a great deal but was quite intelligent when roused. He perspired freely. Painful plantar stimulation elicited a flexor leg response, more marked on the left side, without any definite movement of the great toe. Sharp and blunt points were correctly appreciated on the head, neck, chest and upper limbs. The skin over the abdomen was insensitive. Sharp was interpreted as blunt on both lower limbs.

By February 26 drowsiness had disappeared. The man was incontinent of urine and he complained of pains in the legs; in the left foot he had limited power of voluntary movement. Plantar stimulation elicited an extensor great toe and a flexor leg response, more obvious on the left side. Facial palsy was no longer apparent. Arms were equal in strength. No area of the body was now insensitive to light touch, but thermal sense was imperfect on the lower extremities and absent on the trunk below the nipple level.

Examination of cerebrospinal fluid revealed 102 red cells and 29 white cells, all small lymphocytes, per c.mm.

The fluid contained sugar, 66 mgm. per cent.; chlorides, 731 mgm. per cent.; and protein, 0.035 per cent. The Nonne-Apelt test was negative.

On February 27 dribbling incontinence of urine (containing albumin) and faeces became established. The patient could now move both feet. The following night the temperature was above normal for the last time.

On March 1 signs of mental change became apparent. The man began to make curious statements, asserting, for example, that he had not slept for a week. He was still unable to raise his head or trunk. In the lower limbs movement was limited to the feet, but obvious though ineffectual contractions of the thigh muscles occurred on voluntary effort.

On March 3 the patient at first sight seemed bright and intelligent. In the course of conversation, however, he showed signs of a disordered imagination in remarkable and chiefly grandiose statements which were obviously untrue. His memory for recent events was good.

He now passed urine reflexly and unconsciously at intervals; faeces also were voided without his knowledge. The grip was stronger and equal on the two sides. Power was returning to trunk and legs. Each leg was withdrawn from plantar stimulation and the left great toe gave an extensor response. The right knee-jerk could just be elicited. Pin-prick was everywhere appreciated.

On March 6 the patient talked more rationally but was excitable and emotional. Power had increased in the lower limbs. He possessed some knowledge of impending micturition but lacked inhibitory power. On March 8 rectal sense begun to return.

By March 12 the man seemed mentally normal. He could stand with support and make a few steps. The upper limbs were normal. Knee and ankle jerks were absent, plantar responses extensor. Sensation was normal apart from some loss of thermal sense on the feet and legs. A few days later pus and *B. coli* appeared in the urine; this infection lasted for about three weeks.

By March 18 knee-jerks, ankle-jerks and ankle-clonus were present. Plantar responses were extensor; abdominal reflexes absent. Sphincter control was returning gradually. The patient denied any knowledge of his earlier irrational statements.

On April 24 the man was discharged from hospital in a nearly normal condition. There was some spastic weakness of the lower limbs with exaggerated tendon reflexes, extensor plantar responses and absent abdominal reflexes, and sphincter control was not entirely reliable.

The father, mother, sister and two brothers of the patient followed him to hospital with uncomplicated attacks of smallpox.

Case 5.—G.B., an unvaccinated boy aged 15, had suffered previously from chickenpox, measles and diphtheria. On February 9, 1930, he fell ill with headache and malaise, and on 14th was admitted to hospital with a modified

smallpox eruption (type six) estimated to be at the fourth day of development. The temperature was 99° F. but fell to 98.4° F. on the following day. During the afternoon of February 16 the boy complained of frontal headache, and at night the temperature was 99° F.

On February 17 the patient had slept soundly but awoke with more pronounced headache. He was drowsy, responded unwillingly to questions, and resented interference. Head retraction, Kernig's sign, and tache cérébrale were present. The cranial nerves were normal. The abdominal reflexes were absent; Babinski's sign was present on each side; the left knee-jerk was sluggish and the right was not obtained. Lumbar puncture was performed. In the cerebrospinal fluid no tubercle or other organisms were seen, and cultures were sterile. The fluid contained 490 cells per c.mm., 87 per cent. polymorphs., 8 per cent. small lymphocytes and 5 per cent. large mononuclears; sugar 85 mgm. per 100 c.c., chlorides 743 mgm. per 100 c.c. and protein 0.076 per cent. The Nonne-Apelt test was negative. The Wassermann reaction was negative in cerebrospinal fluid and blood. The blood contained 42 mgm. urea per cent.

At night, temperature 103° F., pulse 144, respiration 40. Occasionally the patient moved the head and arms but mostly lay still with laboured breathing, saliva running from the mouth, and profuse perspiration on the head. It was impossible to rouse him. The pupils were equal in size and reacted to light; an intermittent bilateral convergent strabismus was present. Head retraction had diminished. The upper limbs had a certain rigidity; the legs were flaccid and motionless. Abdominal reflexes and tendon-jerks were absent. Strong stimulation elicited extensor plantar responses. Anæsthesia to pin-prick was complete up to the nipple level. Urine, obtained by catheter on account of retention, was free from abnormal constituents. Clear cerebrospinal fluid under increased pressure was withdrawn by lumbar puncture and 15 c.c. human convalescent smallpox serum injected. After a few hours the temperature rose to 105° F. but soon dropped to 103° F.

On February 18 the boy was deeply unconscious; he made no attempt to swallow saliva which dribbled from the mouth. An extreme degree of trismus made it impossible to force open the mouth. The arms, which were moved from time to time, were semi-rigid and flexed at the elbows; spasm, particularly noticeable on attempt to raise the left arm at the shoulder, relaxed before repeated passive movement. The head and lower extremities remained motionless. A large bulla had arisen spontaneously over the left external malleolus. Lumbar puncture was performed in the evening and clear fluid under considerable pressure withdrawn.

On February 19 the boy was comatose and immobile; breathing was quiet but marked by an occasional deep sigh. Trismus was less marked and strabismus no longer apparent. All the limbs were flaccid and devoid of tendon reflexes. In spite of careful nursing, fresh bullæ had appeared over the heels and back. Lumbar puncture was repeated. Next day, save for incontinence of urine, the clinical condition was unchanged. Lumbar puncture was repeated.

On February 21 the patient was incontinent of fæces; he moaned occasionally. Lumbar puncture yielded clear fluid with yellowish tinge; 8 c.c. human convalescent serum were injected. On February 22 the patient again perspired freely about the head and excessive salivation was apparent, though swallowing was possible with difficulty.

On 23rd the boy repeatedly opened the eyes but remained unresponsive to stimulation. On 24th movement in response to pin-prick included rolling of the eyes and slight jerking of the head. Trismus was less marked and swallowing easier. The arms, especially the right, were again rigid. On 26th the boy moved the arms slightly and when addressed in a loud voice groaned as though attempting to reply. On 27th an intermittent bilateral convergent or divergent strabismus was again evident and was present at intervals for several days. Lumbar puncture was repeated. The fluid withdrawn on February 24 contained 42 cells per c.mm., 91 per cent. small lymphocytes and 9 per cent. large mononuclears; sugar, 95 mgm. per 100 c.c.; chlorides, 778 mgm. per 100 c.c.; and protein, 0.085 per cent. The Nonne-Apelt test was negative.

On March 1 the patient could move head and arms and make groaning attempts to speak. On the right side an extensor plantar response was present; on the left side plantar stimulation elicited weak contraction of the thigh muscles without movement of the foot or great toe. Lumbar puncture was repeated next day.

On March 3 dribbling incontinence ceased and urine was passed unconsciously in small quantities once or twice an hour; it contained some albumin but was free from pus. Retention of fæces alternated with incontinence. The boy was regaining consciousness slowly. Trismus persisted but the patient was able to swallow small quantities of liquid from a spoon. Cerebrospinal fluid withdrawn on March 4 contained 12 cells per c.mm., all small lymphocytes; sugar, 90 mgm. per 100 c.c.; chlorides, 760 mgm. per 100 c.c.; and protein, 0.06 per cent. The Nonne-Apelt test was negative.

On March 6 the patient appeared to understand what was said to him but was still unable to speak; in spite of great efforts to do so the only result was a moaning noise. Voluntary movement of the upper limbs was very limited and the grip exceedingly weak. Some voluntary movement was possible in the right foot. Babinski's sign was present and more marked on the right side. Pin-prick was appreciated except over the left lower extremity. Next day the boy was still unable to articulate but made loud noises in his efforts to form words; his state was highly emotional.

On March 9 articulation had improved to the extent that words were mostly intelligible, though possessed of a groaning quality; there was no special difficulty in pronouncing any letter of the alphabet. The boy was bright and alert but was very emotional. His memory for recent and remote events was surprisingly good and he gave an estimate, approximately correct, of the duration of unconsciousness. He could turn his head but was unable to lift it from the pillow. All movements of the right arm could be carried out

voluntarily but weakly; in the left arm slight movement at the wrist alone was possible. He complained of pain in these limbs. He was able to move the right foot and contract the thigh muscles, but on the left side voluntary power was wholly lacking. Anæsthesia to light touch prevailed over the buttocks and sacrum and over the left lower extremity where pin-prick also was appreciated as a blunt sensation. Thermal sense was deficient over both lower limbs. Wasting was marked.

By March 11 the boy talked incessantly. He began to suffer from delusions. He imagined that one of his nurses had fallen and cut her head, and maintained that he had something in his left arm put there by the nurse each night, and which he demanded should be removed. So persistent was this latter obsession that one was led to consider whether he had any recollection of a few hypodermic injections of atropine given at a time when he was salivating excessively and when he was thought to be in a profoundly unconscious state. Two days later cystitis occurred as a complication.

By March 18 articulation was normal. The patient was quieter and less emotional but had assumed the attributes of a spoiled and naughty child. He was unwilling to move the left arm, particularly at the shoulder-joint, persisting that it pained him when touched. Free voluntary movements at finger, wrist and elbow-joints and limited movements at the shoulder were possible. Power had improved considerably in the right arm, though fine finger movements were not possible; an intention tremor was present. Lateral nystagmus was noted. The patient could write in a clumsy fashion. Masturbation became a troublesome feature.

By March 26 the mental state was almost normal and the boy expressed regret for his earlier misdeeds. He now spoke with a stammer, an old impediment for which he had attended a speech clinic; this had been present on admission to hospital, absent during the loquacious and emotional stages of the illness, and had returned with improvement in the mental state. Bladder and rectal control had increased. The right arm was stronger and intention tremor no longer present. The grasp of the left hand remained weak, but movements of the forearm and at the shoulder-joint were free and pain was absent. Power in the trunk muscles had increased and the patient could make an effort to stand; the left leg was still weaker than the right. Both knee-jerks were present. Cutaneous sensibility was almost normal.

On April 2 the boy could place his left hand on the top of the head; an intention tremor was now present in this limb. On April 8 the right upper abdominal reflex was obtained, and on April 10 both right reflexes.

While strength increased and he was able to walk, the mental and moral state regressed, and again he became wilfully naughty, recommenced masturbation, and seemed determined to make no effort to regain control over his sphincters. His old trophic lesions again broke down and a new one appeared over the right great trochanter, necessitating a return to bed.

The patient was eventually discharged from hospital on June 6. At that time incontinence had not occurred for two weeks and the behaviour had for

some time been consistently good. Wasting of the left arm was apparent, a coarse intention tremor was present, and fine movements could not be performed with the fingers of that limb. Otherwise power and movement in the upper extremities were good, and all tendon reflexes were obtainable. At times a lateral nystagmus was present. The left lower abdominal reflex was absent. Power was good in the lower limbs and the boy walked well. Tendon-jerks were present, on the left exaggerated and with ankle clonus. The left plantar response was extensor, the right indefinite. Sensation was normal. Trophic lesions had healed. The urine was free from abnormal constituents.

The patient was seen again on May 31, 1931, nearly a year later, when he cycled from his home about twelve miles away. Since his discharge he had worked continuously as a barber's assistant. Mentality appeared normal, though the rather excitable, nervous manner was still evident and the stammer persisted. Power was normal in the limbs and fine movements of the fingers were well performed. The right tendon-jerks were present, the left slightly exaggerated with ankle clonus. The left plantar response was extensor, the right indefinite. Nystagmus and intention tremor were absent.

Case 6.—K. C., an unvaccinated girl aged 7, had suffered previously from measles, chickenpox and diphtheria. On April 12, 1931, she fell ill with headache and pain in the limbs, and a smallpox rash appeared on 14th.

On April 19 the patient was admitted to hospital with a pustular modified smallpox rash (type six). Temperature 102° F., pulse 96, respiration 22. She was feverish and complained of headache; a follicular deposit was present on each tonsil. No abnormality was found on examination of the heart, but in the lungs a diffuse bronchitis and signs of early pneumonia at the right base were detected. A culture from the throat showed no diphtheria bacilli.

At 11.30 p.m. the patient was unconscious; she groaned but could not be induced to speak. There was retention of urine. The limbs were moved in response to stimulation and there was, apparently, no anaesthesia. Dysphagia and trismus were present; the palate moved normally. The pupils were equal in size and reacted sluggishly to light; an intermittent divergent strabismus was noted. Corneal reflexes were present, abdominal reflexes absent. The knee, but not the ankle-jerks were obtained; plantar responses were flexor. Head retraction and Kernig's sign were absent. Lumbar puncture readily yielded clear, colourless fluid.

On April 20 the girl was deeply unconscious, slightly cyanotic, and quite unable to swallow. Trismus was well-marked but squint was no longer evident. The head was a little retracted. The limbs were moved sluggishly in response to stimulation. Tendon reflexes were present in the arms only. True incontinence of urine was present.

At 1 p.m. 15 c.c. of cerebrospinal fluid were withdrawn by lumbar puncture. and 10 c.c. of convalescent smallpox serum injected. In the fluid no tubercle bacilli were found but cultures gave a pure growth of *Staphylococcus aureus*, which appeared to be a contamination. There were 339 red blood-cells, and 36 leucocytes per c.mm., 30 per cent. polymorphs., 64 per cent. small

lymphocytes, and 6 per cent. large mononuclears; sugar, 95 mgm. per 100 c.c.; chlorides, 702 mgm. per 100 c.c.; and protein 0.02 per cent. The Wassermann reaction was negative.

At night, temperature 104.4° F., pulse 110, respiration 38. Dyspnoea increased, cyanosis was more marked and the pulse showed signs of failing. The lungs were full of coarse bubbling râles. Death occurred at 6.30 a.m. on April 21.

Three sisters and two brothers of this patient contracted smallpox from her but experienced only minor complications. The mother of the family, who had been vaccinated in infancy, was successfully re-vaccinated and admitted to hospital with the youngest child whom she was nursing; she remained in good health.

Pathological examination.—Macroscopically the brain showed only congestion. Cultures yielded a short-chained streptococcus; later, in histological preparations, the vessels in many of the organs were seen to be filled with similar organisms indicative of a terminal bacteriæmia. The lungs were the seat of diffuse bronchitis with early bronchopneumonia at the right base.

Microscopically, typical lesions exist around the vessels, especially the veins, and are roughly symmetrical in the two hemispheres. Meningeal infiltration is limited to small areas where mononuclear cells are collected in the meshes of the pia-arachnoid. Perivascular infiltration with large and small lymphocytes and a few large mononuclears is of moderate intensity; around many vessels only a single layer of cells is present, around others the ring is three or four cells deep. In the extra-adventitial tissues the usual broad zone of microglial cells, some with highly polymorphic nuclei and a few showing karyorrhexis, includes also scanty lymphocytes, and is accompanied by demyelination and the appearance in the phagocytic cells of tiny granules of Scharlach-staining material.

Such changes are of medium severity throughout the white matter of the hemispheres and in the cerebral cortex, where an extra-adventitial infiltrate is more diffuse and less sharply delimited peripherally. Mild lesions are present in the caudate nucleus, globus pallidus and anterior part of the putamen, severe lesions in the posterior part of the putamen, claustrum and capsulæ externa and extrema. Lesions are less marked in the brain-stem than is often the case, and the white matter of the cerebellum is only slightly affected.

Most segments of the spinal cord are normal; of twelve levels examined only four from the upper dorsal and lumbar regions show typical changes. In a few of the remaining sections some swelling of the myelin sheaths, unaccompanied by cellular infiltration, is apparent at the periphery of the cord or along the lips of the anterior fissure.

In all parts of the central nervous system the nerve-cells are well-preserved or, where situated in a densely infiltrated zone, exhibit only mild degenerative changes.

Of the other organs, the liver shows well-marked mononuclear infiltration around the vessels of the portal tracts, and mild fatty changes of diffuse

distribution in the liver cells. The spleen is greatly congested. The left lung is congested and oedematous, with bronchitis in some of the smaller tubes but no bronchopneumonia; the right is the seat of a definite bronchopneumonia.

Case 7.—The following case occurred at Stoke-on-Trent. For the ensuing clinical account and for permission to include it in this series we are indebted to Dr. A. J. Ewing.

On April 14, 1930, W. B., an unvaccinated boy aged 13, fell ill with headache, backache, and vomiting. On 18th a smallpox rash was noticed, and on 19th the boy was admitted to hospital; the eruption was mild and there were no general symptoms.

On the morning of April 22 the lad appeared quite normal. At 12.30 p.m. he was thought to be asleep and no attempt was made to waken him; later in the afternoon it was found that he could not be roused. He lay relaxed with legs slightly flexed and without head retraction. The arms were flexed and stiff; the wrists were strongly flexed with thumbs held in the palms between the second and third fingers. There was some resistance to passive movement at shoulder- and elbow-joints, and to a less degree at the wrist. The pupils were equal and reacted to light, but varied in size from time to time; there was no nystagmus, squint or ptosis. Knee-jerks were absent and there was no ankle clonus; plantar responses were flexor.

Between April 22 and 24 the clinical condition remained almost unchanged. Faeces were retained; urine was passed involuntarily. Swallowing was difficult. The only response which could be obtained from the boy was a faint groan when attempts were made to extend the arms. The head remained freely movable. On 23rd 8 c.c. clear fluid under normal pressure was withdrawn by lumbar puncture; after centrifuging only an occasional polymorph was seen. On 24th the patient showed signs of collapse. Temperature 102° F., pulse 126.

On the morning of April 25 the patient lay on his back as before; he was unconscious and breathing stertorously. The neck and the legs were free from rigidity; the arms had at first a certain stiffness, disappearing after repeated passive movement. All reflexes were absent from the right arm and leg; on the left side knee-jerk, plantar response and triceps-jerk could just be obtained. The pupils reacted briskly to light; they were regular and equal but varied in size at different examinations. The boy was emaciated and swallowed only with difficulty. Death occurred during the day.

Pathological examination.—The chief macroscopical findings were intense congestion of the brain, particularly marked in the white matter, and congestion of both lungs with capillary bronchitis and areas of bronchopneumonia at the base. Cultures of brain and blood proved sterile.

Histologically the lesions are typical and are identical with those occurring after vaccination. In many parts of the nervous system both arteries and veins have mild perivascular cuffing with lymphocytes and a few large mononuclear cells; sometimes a few lymphocytes may be found also in the nervous substance outside the vessel wall. Small patches of meningeal infiltration with similar cells occur in places. Many of the veins are surrounded

PLATE VII.



FIG. 1. *Case 1.*—Perivascular demyelination in white matter of cerebral hemisphere. Weigert-Pal.

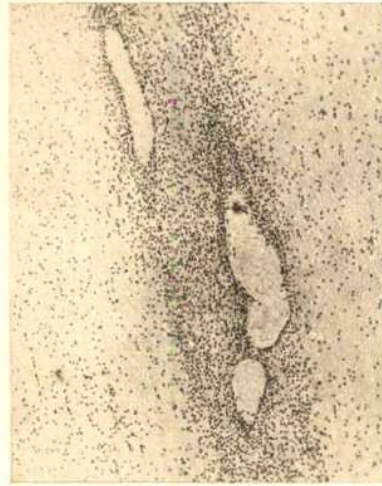


FIG. 2. *Case 7.*—Low-power view of affected vessels in white matter of cerebral hemisphere. Iron - alum - hæmatoxylin and eosin.



FIG. 3. *Case 7.*—Drawing from a Bielschowsky preparation of a zone of perivascular demyelination. Although many of the axis cylinders show degenerative changes, these structures are not completely destroyed as are the myelin sheaths.

To illustrate paper by J. Pickford Marsden and E. Weston Hurst.

by a broad extra-adventitial zone of cellular infiltration associated with complete demyelination of the nerve-fibres; in stained sections these lesions are readily visible to the naked eye. (Fig. 2.) Not infrequently coalescence of the zones around adjacent vessels has taken place. The cellular reaction here is almost wholly microglial, though a few glial cells with swollen nuclei are also present. In spite of the extensive destruction of myelin sheaths, fatty granules are far from abundant. The axis-cylinders passing through the demyelinated zones often show swellings and varicosities, but are not completely destroyed as are the myelin sheaths. (Fig. 3.) Where the grey matter is involved, some chromatolysis without nuclear changes may be present in the nerve-cells; more severe degeneration is not observed and no outfall of nerve-cells is apparent.

These lesions are well marked in the white matter of the cerebral hemispheres and in parts of the cortex, although in the latter simple perivascular cuffing is more commonly encountered. The island of Reil is most heavily involved. The basal ganglia are particularly severely affected; the caudate nucleus, lenticular nucleus and optic thalamus all contain extensive lesions. In the mid-brain and pons lesions are scanty, and the medulla, cervical and upper dorsal cord are wholly free from abnormality. Changes reappear in the lower dorsal cord and below that increase to a maximum in the lumbar region where they are very intense and affect both grey and white matter. The zone of demyelination so frequently seen beneath the ependyma of the lateral ventricles is of very limited extent in this case, and, except in the lumbar region, no strip of demyelination is seen at the periphery of the cord or along the lips of the anterior fissure.

The lungs contain areas of capillary bronchitis and early bronchopneumonia. The liver shows some congestion, especially in the central parts of the lobules. The other organs present no definite microscopical abnormality.

Group II.

Between September, 1929, and February, 1930, five cases of acute perivascular myelinoclasia occurred amongst 2,400 patients admitted to the London smallpox hospitals. During the same period eight other patients exhibited a syndrome characterized by drowsiness and pyrexia. Though commonly this state was transient and abnormal physical signs scanty, the symptoms suggested mild or abortive attacks of the above malady, and the cases were tentatively classed as "borderline cases." This suggestion gained strength from the absence of any other demonstrable complication or intercurrent disease to account for the symptoms, from the temporal relation to the attack of smallpox, which was that of acute perivascular myelinoclasia, and from the fact that the cases were encountered only about the time when the latter disease was occurring in the hospital. Careful observation of over 8,000 cases of smallpox

before and since this period has failed to reveal further examples. In all the "borderline cases" symptoms were so mild and transient that lumbar puncture was considered unjustifiable.

The following case is recorded as being fairly typical of the whole group; here symptoms commenced on the seventh day of the rash.

Case 8.—E. H., a girl aged 14, was primarily but unsuccessfully vaccinated on January 6, 1930, when her father and sister were removed to hospital with smallpox. On 9th she complained of headache and malaise; on 11th a smallpox rash made its appearance. The patient was admitted to hospital on 15th with a discrete pustular modified eruption (type six). The temperature was 98.4° F. and there were no general symptoms.

On the morning of January 17 the ward sister reported that the child had felt faint. She was in a drowsy state and resented being roused; with difficulty she could be persuaded to reply to questions. Absence of the right knee-jerk and of both ankle-jerks were the only abnormal physical signs. When seen again about half an hour later the child spoke intelligently and had almost completely lost her stupor.

Later in the day, temperature 98.4° F., pulse 104, respiration 24. The girl again became very drowsy but it was possible to rouse her to answer questions. The bowels had not been opened during the day; the patient had passed 5 oz. of urine (free from abnormal constituents) and the bladder was not palpable.

On January 18 the girl was free from symptoms. On examination, absence of knee-jerks was the sole abnormality noted. At night the temperature rose to 101° F., but resumed the normal level on the following morning.

The knee-jerks remained absent for a time; apart from this convalescence was uneventful.

The following case, which appears definitely to belong to the first group, is included here rather than there as occupying a position intermediate between the cases of acute perivascular myelinoclasia detailed already and the "borderline cases" typified by the one just recorded. Though more pronounced than in the last case, symptoms, commencing on the tenth day of the rash, were mild, and in a week from the onset the patient had apparently recovered completely. With this link connecting the two groups, and in view of the facts stated as introduction to the preceding case, it seems impossible to escape the conclusion that the "borderline cases" represent abortive attacks of the morbid condition responsible for the graver illnesses of the first group of cases.

Case 9.—J. F. H., an unvaccinated boy aged 14, gave no history of previous illness. On October 10, 1929, he suffered from headache and malaise; a smallpox rash appeared on 13th. On 20th he was admitted to hospital. His

eruption (modified, type six) was commencing to crust; pyrexia and general symptoms were absent.

On October 22, temperature 100° F. The patient vomited on several occasions and was drowsy. Apart from conjunctivitis in the left eye nothing abnormal was discovered on physical examination.

On October 23 the patient was incontinent of urine and faeces, very drowsy and strongly resentful of interference. He lay curled up on his left side with knees drawn up. He complained of severe frontal headache. The pupils were equal and reacted to light. Abdominal reflexes were absent, knee-jerks brisk, and plantar responses extensor. Kernig's sign was positive but the head was not retracted. Clear cerebrospinal fluid readily escaped on lumbar puncture. At night short periods of restlessness were interposed but the boy's state was mainly one of stupor.

On October 24 the boy was more rational and submitted more readily to examination, but he was still somnolent and maintained his characteristic curled-up attitude. Incontinence had ceased and the urine now contained a trace of albumin. The cranial nerves and optic discs were normal. Abdominal reflexes were elicited with difficulty; knee-jerks were normal, plantar reflexes extensor. Kernig's sign was present. On the outer aspect of the right thigh appreciation of light touch and thermal sense were deficient. Lumbar puncture yielded clear fluid under apparently normal pressure. Cultures were sterile. The fluid contained 58 cells per c.mm., all small lymphocytes; sugar, 58 mgm. per 100 c.c.; chlorides, 708 mgm. per 100 c.c.; and protein, 0.18 per cent.

On October 25 abdominal reflexes were readily obtained; plantar responses were flexor; knee-jerks could not be elicited. The blood-urea was 37 mg. per 100 c.c. On October 26 the patient was still drowsy and after examination curled up and went to sleep. The left knee-jerk was obtained with difficulty. The urine contained albumin and acetone.

On October 28 the boy again complained of headache; examination of the nervous system revealed no abnormal physical signs. On 29th headache had disappeared and on 30th the condition of the urine was normal.

Progress hereafter was uneventful and the patient was discharged from hospital in apparently normal health on November 28. Cerebrospinal fluid withdrawn on November 9 contained no organisms, 7 cells per c.mm., all small lymphocytes; sugar, 55 mgm. per 100 c.c.; chlorides, 737 mgm. per 100 c.c.; and protein, 0.05 per cent. The Nonne-Apelt test was negative.

An acute toxic or hæmorrhagic encephalitis may occur in the course of focal or general pyogenic infection (Brain, 1928), or during an attack of a specific fever, especially measles and scarlet fever; sometimes the nature and source of the toxæmia may be obscure (Brain, Hunter and Turnbull, 1929). The highest incidence of this type of encephalitis in the acute specific fevers is among severe cases, e.g., cases of hæmorrhagic measles, and symptoms commonly appear when toxæmia is at its height.

In this respect it differs from acute perivascular myelinoclasia, the incidence of which is not determined by the severity of the exanthem, and which usually manifests itself at the end of the first week of the primary illness when the patient has commenced convalescence.

During the last two years one of us (J. P. M.) has seen two patients in whom the onset of smallpox was marked in an unusual manner by nervous symptoms possibly due to such an acute toxic encephalitis. In each case symptoms were present during the toxæmic stage and disappeared rapidly as that phase of the illness passed; to the clinical state the term "meningismus" might have been applied. A description of one of these cases is given here. For details of the child's condition prior to admission to the smallpox hospital we are indebted to Dr. F. Young.

Case 10.—E. N., an unvaccinated girl aged 6, had suffered previously from measles. On February 23, 1930, she vomited, complained of headache, and appeared drowsy, and on 24th was admitted to a children's hospital. She could be roused only with difficulty. The neck was slightly rigid and Kernig's sign was present. The pupils reacted to light. The limbs were flaccid; tendon reflexes were sluggish but all were present except the right knee-jerk; plantar responses were extensor. No coagulum formed in the cerebrospinal fluid which contained 0.68 per cent. chlorides and 0.02 per cent. protein.

On February 25 the patient was more conscious but lay in a semiflexed attitude. Physical signs were unchanged. The blood contained 7,000 white cells per c.mm. The urine was free from abnormal constituents.

On February 26 a smallpox eruption began to appear, and the reflexes returned to their normal condition. On admission to the smallpox hospital later in the day the patient was still a little drowsy; otherwise, on examination of the nervous system, no abnormal physical signs were found.

On March 1 the girl still slept a good deal. She could stand unsupported, but appeared rather unstable and took a few steps apprehensively in a waddling fashion on a wide base. The eruption was modified and of type 5 (between 100 and 500 lesions on the face).

On March 4 the patient could stand and walk naturally. Later she developed keratitis, but otherwise subsequent progress was uneventful.

The following case is unique among the records of 15,000 patients admitted to the London smallpox hospitals between 1893 and 1927. This man suffered from an acute myelitis which, commencing on the fifth day of rash, involved the optic nerves and the medulla, and led to death four days later. Unfortunately there is no record of any post-mortem examination.

Case 11.—J. E., a man aged 46, had one small scar due to vaccination in infancy. On June 22, 1899, he developed symptoms which he described as

those of a violent cold. On June 25 a smallpox eruption began to appear, and on 28th the patient was admitted to hospital; the rash was vesicular and discrete, with hæmorrhagic areolæ around many of the lesions. The temperature was 100° F. and continued to rise until shortly before death it reached 104° F.

On June 29 the man was very excited and restless and felt that he could not keep still in bed. He complained of strange sensations in his legs and abdomen, which came on in paroxysms and caused much distress. He also complained of dimness of vision. The following notes were made on this day by the late Dr. T. F. Ricketts.

"10 p.m. The patient's excited and restless condition was due to no mental change but consequent only on his sensations. The condition got worse up to 7 p.m., when the unendurable sensations in his legs recurred every minute or two. The patient was partially collapsed, with small quick pulse, perspiring skin, &c. He was forced to sit up in bed with his legs drawn up, sweating and groaning. Every few minutes the exacerbation of sensation recurred and seemed to give unendurable distress. At these times he clasped or rubbed the seat of pain; in the intervals he seemed to have uneasy sensations elsewhere, generally in the abdomen, sometimes in the back. The patient would never call the sensation "pain"; he referred to it as "numbness," "cramps," "tingling," but seemed satisfied with no epithet. During the paroxysms and in the intervals, the muscles of the part affected were quite relaxed. The part affected was sometimes the left calf, sometimes the dorsum of the left foot, sometimes the other leg. The arteries of the legs and feet beat normally at all times and were equal in the two legs. There is no anæsthesia. Dimness of vision has increased. When first seen (about 3.30 p.m) there was an indistinct perception of objects, so that he could distinguish where a person was standing but could not count fingers held in front of his eyes. There was no hemianopia, but incomplete amaurosis equal in the two eyes. This became worse, and at 7 p.m. he was totally blind and had no perception of light and darkness. Eye reflexes tested at 3 p.m.; pupils dilated; slight sympathetic pupil reflex; no proper reaction to light, in fact when the eyes were closed the pupils contracted slightly and on opening the eyes they slightly dilated and oscillated a little; in consequence of the defective vision the convergence test could not be made. At 10 p.m. there was slight ptosis of the right lid (not noted before). Ocular movements were then examined. The patient when told to move his eyes in a given direction, moved his head, and when his head was held the eyes moved slowly to the required limits, but upward and downward movements were distinctly defective in extent. When moving the eyes to the right or left there was slight external strabismus at the limit of movement. The left eye was examined and the retina was normal; there was optic neuritis, redness and blurring of the disc, but no tortuosity of the vessels and no perceptible swelling. In consequence of the ptosis of the right

eye and the defective movement, the right disc could not be seen, but the lower part of the retina was normal."

On July 1 the patient was clear-headed and in no pain. Examination of the chest revealed nothing abnormal except an area of impaired resonance at the right base. Inspiration was laboured, the muscles of extraordinary respiration being brought into play, and there was some difficulty in swallowing. In the evening respiratory distress was more marked and cyanosis was evident. It was then found that the patient had no power to move his legs, neither could he feel them; only when attended to could he "feel his legs numb." Retention of urine and incontinence of faeces were present.

On July 2 the man's condition was worse, and he died early on the morning of July 3.

General Remarks on Recorded Cases.

We have no definite information of the true nature and pathology of the nervous condition in Case 11. It occurred as an isolated case among many thousands of patients suffering from smallpox, and the symptomatology differed from that presented by the cases of acute perivascular myelinoclasia observed recently; the time of onset in relation to the attack of the exanthem was within the limits of the "incubation period" of such cases. More particularly on account of the involvement of the optic nerves this case invites comparison with others recorded under the title of neuroptico-myelitis or Devic's disease.

Case 10 is not considered to bear any relationship to the remainder of the series. From evidence afforded by the symptomatology, and from the fact that the condition appeared during the toxæmic stage of smallpox, it is suggested that it might be assigned to the toxic encephalitis group, which, naturally enough, is but rarely encountered among cases of modified smallpox (two examples among 11,000 cases in our series).

Case 9 almost certainly represents a mild attack of acute perivascular myelinoclasia, but since in the intensity of its manifestations it differed so markedly from the typical cases, with regard to statistics, &c., it has been considered separately.

The significance of the group of cases of which Case 8 is quoted as an example is admittedly questionable. Nevertheless, the facts we have already mentioned, and particularly the temporal association of these cases with the typical disease, suggest the possibility that abortive cases of acute perivascular myelinoclasia may occur.

Cases 1 to 7 form a homogeneous group, of which the three fatal cases exhibited histological changes typical of acute perivascular myelinoclasia. The remaining four suffered severely, but recovered more

or less completely; in two of these symptoms were predominantly spinal. The average age of the patients attacked was 12 years, with extremes of 7 and 21; five were males and two were females. The period elapsing between the commencement of the outcrop of the focal rash and the onset of nervous symptoms varied between five and thirteen days, with an average of slightly more than seven days.

All patients in this series suffered from modified smallpox; this modification was due primarily to the benign nature of the strain of causative virus. With the exception of the third patient, who suffered from concurrent vaccinia and variola, all were unvaccinated.

In no instance was there evidence of case-to-case spread of the nervous condition, which never affected more than one member of a variolous family; each case appeared to arise spontaneously, though more or less contemporaneously with others.

Six cases occurred between the beginning of September, 1929, and the end of April, 1930. One of these was at Stoke-on-Trent, and five were drawn from London boroughs, mainly in the East End, where at that time smallpox was rife. Two of the London cases occurred in January, 1930, and two in February; three of these, two almost simultaneously, occurred in one particular hospital ward. Finally, one case occurred in April, 1931, and came from a London borough.

TABLE I.

Date	London Smallpox Hospitals		Remarks
	Cases of S.P. admitted	Cases of A.P.M.	
1928	290	0	
1929—			
1st quarter ..	279	0	
2nd „ ..	1,020	0	Troup and Hurst's case occurred at Willesden in June
3rd „ ..	602	1	Occurred in September
4th „ ..	1,178	1*	Occurred in October
1930—			
1st quarter ..	2,623	4	Two in January; two in February at two days' interval in one ward
2nd „ ..	2,189	0	Stoke case (No. 7) occurred in April
3rd „ ..	671	0	
4th „ ..	750	0	
1931—			
1st quarter ..	874	0	
2nd „ ..	789	1	Occurred in April
3rd „ ..	198	0	

* Mild case (No. 9).

TABLE II.

Year.	England and Wales		
	Cases of S.P.	Deaths	Cases of A.P.M.
1928	12,420	58	0
1929	10,987	89	*3; 1 fatal
1930	11,889	28	5; 2 fatal
1931 (to Sept. 30) ..	5,028 (to June 30)	8	1 fatal
	40,254	128	9; 4 fatal

* Including one mild case (No. 9 in this paper).

TABLE III.

Date	England and Wales	
	Vaccinations* (with Govt. lymph)	Cases of A.P.M.
1922-1927	—	93 (including suspected cases)
1928—		
1st quarter	162,579	19
2nd „	145,898	28
3rd „	75,835	4
4th „	65,788	4
1929—		
1st quarter	60,068	4
2nd „	170,813	13
3rd „	61,494	8
4th „	60,457	2
1930—		
1st quarter	85,620	4
2nd „	74,079	1
3rd „	68,808	1
4th „	56,264	0
1931—		
1st quarter	Not available. Writer's personal estimate at roughly	1
2nd „	200,000	8
3rd „		1
	1,286,658	93

* An unknown percentage, probably about 80, of the total vaccinations in this country are performed by private practitioners using proprietary lymphs, so that the above figures represent about two-thirds of the real total; in 1929, however, the S.S. "Tuscania" scare was responsible for much extra private vaccination.

This chronology and the relation of the cases to the prevalence of smallpox are shown in Table I. If now comparison is made between, say, the incidence of smallpox during the first and second quarters of the year 1930, it is clear that the frequency of the nervous disease is

not related to that of the exanthem. In Table II we show the total number of smallpox cases notified in England and Wales during the same period, their mortality-rate, and the incidence of acute perivascular myelinoclasia in the country as a whole. Since all examples of the nervous condition, save the Stoke case, were drawn from the London area, the figures in Table I give an erroneous impression of its frequency. It may be interesting to add in Table III figures of the incidence of the post-vaccinal disease, which at present appears to be becoming increasingly infrequent; again the lack of direct relation between the number of vaccinations and the incidence of acute perivascular myelinoclasia is apparent. It is impossible to compare the relative incidence of the nervous condition after vaccination and after smallpox, for the majority of primary vaccinations are performed in infancy, an age-period almost, if not quite, free from acute perivascular myelinoclasia. But it is important to realize that discontinuation of vaccination would not necessarily lead to disappearance of acute perivascular myelinoclasia, were the predisposed individuals to acquire as a result an attack of smallpox.

Treatment with Convalescent Serum.

Horder (1929) successfully vaccinated a boy aged $4\frac{1}{2}$ years, and at the same time successfully re-vaccinated the mother. On the eighth day the boy became drowsy, and on the eleventh day was stuporous. On the fifteenth day 5 c.c. of the mother's serum was injected intrathecally into the child, who subsequently made a good recovery.

Hekman (1930), with fourteen recoveries out of sixteen patients treated, and Grüneberg (1930), with two patients, both of whom recovered, have since claimed good results in the treatment of post-vaccinal encephalitis from the employment, mainly by the intravenous route, of the serum or citrated blood of convalescents from vaccinia. In one case the serum was obtained from a man vaccinated four years previously.

The publication of Horder's article suggested the use of smallpox convalescent serum on our variolous encephalitics, and as a supply of serum had already been collected from patients at about the fourth week of numerically severe attacks of modified smallpox, the first case (No. 3 in this paper) was so treated. (It will be remembered that this case suffered from concurrent variola and vaccinia and recovered.) Of the seven severe cases of acute perivascular myelinoclasia, four received serum in doses of from 10 to 22 c.c.; three, in one of which symptoms were predominantly spinal, recovered, and one died. Of the three not treated

with serum, one with predominantly spinal symptoms recovered and two died.

It is obvious that the number of cases in this series is too small for any far-reaching inference to be drawn therefrom. However, in attempting to assess the value of any therapeutic measure in cases of this disease the following facts should be borne in mind: that, clinically at least, two types of the condition (encephalic and spinal) may be recognized; that the case mortality is definitely higher in the encephalic group; and that, in the absence of any "specific" treatment, it is possible to anticipate with a degree of confidence the recovery of a certain proportion of the cases.

If it could be shown that in a large number of cases of acute perivascular myelinoclasia of severe type the recovery rate was much higher among those receiving convalescent serum than among those not so treated, the theory postulating the direct responsibility of the virus of the exanthem for the nervous condition might hold a stronger position than it does. It cannot be said that this has yet been established. Those rejecting this theory can find on theoretical grounds scant support for a principle of treatment with antibodies specific only against the causative agent of the associated disease (vaccinia, variola, measles, &c.), especially when it is remembered that by the time nervous symptoms appear the patient must often already be in possession of such antibodies. On the other hand, similar treatment applied in the toxic encephalitis of, for example, measles, would be expected to yield good results (*vide* Lowenberg and Shaller, 1926). On theoretical grounds it seems possible that, if acute perivascular myelinoclasia is actually an infection, the serum of recovered cases might be employed with advantage if it were at all certain that the donors were free from the causative agent of the condition.

Note on the Pathology and Cerebrospinal Fluid.

We have but few remarks to make on the pathology. In all three fatal cases the lesions were typical of acute perivascular myelinoclasia and were indistinguishable from those in cases following vaccination, of which one of us (E. W. H.) has examined more than a dozen. Only the condition of the lumbar cord in Case 1 is worthy of special mention; here many of the anterior horn cells were necrotic, a distinctly unusual occurrence in the disease under consideration. While, when situated in an area of dense infiltration, the nerve-cells may exhibit mild degeneration, the above-mentioned observation is in our experience without

parallel, though in Troup and Hurst's case the lumbar cord was, at autopsy, in a diffuent state and, had examination been possible, would presumably have shown destruction of nerve-cells.

The laboratory reports on the cerebrospinal fluid, for which we are indebted to Dr. V. D. Allison, supply some interesting information. The early phases of the disease are marked by a moderate or pronounced pleocytosis; the cells may either be wholly lymphocytic (Cases 2 and 9), or they may include a high percentage of polymorphonuclear leucocytes. In the course of a few days the cell-count rapidly falls and mononuclears alone are found. Except in Case 6, the total protein was moderately increased; it did not always fall with diminished cell-content of the fluid, and in Case 2 even showed a rise as late as the sixteenth day. The Nonne-Apelt reaction was invariably negative. The amount of glucose probably showed no significant alteration from the normal (variously given as 45 to 85 mgm. per cent.), though in Cases 5 and 6 the figures were rather high. In Cases 2, 6 and 9, chlorides, estimated as NaCl, were apparently diminished during the early stages; in Case 5, on the other hand, abnormally high figures were obtained on the ninth and seventeenth days. The results of the examinations are set forth in Table IV.

TABLE IV.

Case	Stage	Examination of C.S.F.				Sugar mgm. %	Chlor. mgm. %	Protein %	Nonne- Apelt-
		Cells	Polys. %	Lymph. %	Large mono. %				
2	4 days ..	74		100		64	684	0.07	Neg.
	9 " ..	27		100		62	725	0.07	Neg.
	16 " ..	9		100		62	718	0.14	Neg.
3	2 days ..	{ 488 R. 542 W.	48	53	4	60	749	0.08	Neg.
	6 " ..		22	74	4			0.10	Neg.
4	3 days ..	{ 858 R. 112 W.	1	96	3	80	743	0.10	Neg.
	9 " ..	{ 102 R. 29 W.		100		66	731	0.035	Neg.
5	2 days ..	490	87	8	5	85	743	0.076	Neg.
	9 " ..	42		91	9	95	778	0.085	Neg.
	17 " ..	12		100		90	760	0.060	Neg.
6	2 days ..	36	30	64	6	95	702	0.02	
9	3 days ..	58		100		58	708	0.18	
	19 " ..	7		100		55	737	0.05	Neg

Several patients suffered from albuminuria at a time when no pus was present in the urine, and, in all three cases in which the urea content of the blood was determined, the figure considering the age of the individual was distinctly higher than normal. In fatal cases no renal lesions were detected.

DISCUSSION.

Acute perivascular myelinoclasia possesses a more or less characteristic symptomatology. Although morbid changes are usually widespread, from a clinical standpoint two types of the condition may be recognized, according to the relative intensity of encephalic or spinal symptoms. From a comparative study of the reports of the Vaccination Committee (1928, 1931) and of the literature on cases following smallpox, it seems that among post-vaccinal cases the first type may predominate, while in association with smallpox spinal symptoms are more commonly encountered. Yet even clinically the two types often overlap at some stage and the distinction is rarely clear-cut, though from a prognostic point of view it may have some significance. Even when encephalic symptoms are least prominent and the clinical features suggest a major incidence upon the lumbar region of the cord, some degree of drowsiness is rarely wholly lacking; this was true even of Troup and Hurst's case which, belonging chronologically to the recent outbreak, was both clinically and histologically the most purely myelitic of those occurring during the present decade. In either type the onset of the nervous state, if not sudden, is never insidious, and it follows the primary disease at a characteristic and relatively fixed interval, from ten to thirteen days in the case of vaccination (i.e., between the seventh and tenth days of the course of the vaccinal lesion), from five to thirteen days after the appearance of the focal rash of smallpox, at about the end of the first week in measles, during the second half of antirabic treatment, &c. This similarity of incubation periods is remarkable.

Frequently attention is drawn to the onset more by observation of something unusual in the state or behaviour of the patient than by any complaint on his part. An unsteady gait or unnatural somnolence may arouse suspicion. A rise in temperature from a normal or subnormal level seems the rule, and this fever, usually remittent, persists throughout the acute stages; headache with pain in the back or limbs is a common symptom, and the patient may vomit. In either type of the malady drowsiness is usually soon the outstanding feature, but sometimes irritability may occur. Neck rigidity, Kernig's sign, and tache

cérébrale may be present. The initial condition of the tendon reflexes is not constant; the abdominal reflexes usually disappear early. Disturbances of sphincter control are almost constantly present. In the encephalic type the drowsy state deepens to a stupor from which the patient cannot be roused, and later perhaps to profound coma; the limbs typically become flaccid and the reflexes are abolished, though a condition of clasp-knife rigidity may obtain, more especially in the upper extremities. The plantar responses either cannot be elicited or are of the extensor type. Collective rather than individual paralyses may be present, as paraplegia, pareses of the upper limbs, or facial weakness on one side. Ocular changes are not often found, though there may be temporary inequality of the pupils and intermittent squints; papilloedema had been recorded. Trismus may be extreme, and in the past has been attributed to tetanus; changes in the region of the fifth nucleus may explain this spasm. Sweating about the head and excessive salivation, either real or apparent from dysphagia, may be prominent. This state may in a very few days terminate in death with signs of bulbar involvement and terminal hyperpyrexia; or on the other hand, an apparently moribund patient may make a most unexpected and dramatic recovery. Before death signs of broncho-pneumonia are often present.

If the patient survives the acute stages, the unconscious state may last for days or even weeks. Bed-sores and cystitis are likely to supervene, and together with broncho-pneumonia may lead to death. Our own experience suggests that certain of the "bed-sores" arise as trophic lesions on parts of the body related to the most severely affected regions of the spinal cord; such lesions, appearing first as bullæ, occur early, and their presence on the foot or lower leg (not necessarily over "pressure points") is too likely to be regarded as a result of that undesirable combination, an unconscious patient, a hot-water bottle and a careless nurse.

In the spinal type (e.g., Cases 2 and 4) the patient, at the end of a period which can be measured in days, has lost all signs of drowsiness; in the encephalic type the return of consciousness may be so gradual as to make it doubtful at times whether the patient has regained understanding or not. Certainly at a somewhat later stage his immobility and unresponsive state may be attributed more to a peculiarly inert state of mind than to a lack of appreciation of his environment.

True urinary incontinence may precede return of consciousness, and in paraplegic cases rectal and vesical sense are usually wanting when

the patient reaches a stage of intelligence. Urinary incontinence may commence as a constant dribble, become intermittent as the bladder functions reflexly, and disappear finally with gradual re-awakening of bladder sensibility and increasing voluntary sphincter control. Improvement in rectal and vesical sensibility may be slow, but it usually follows closely upon recovery from paralysis in the lower limbs. Nevertheless a liability to transient, intermittent loss of sphincter control constitutes one of the legacies of the disease.

With the return of consciousness the distribution of paralysis can be determined with greater accuracy. Flaccid paralyses with absent reflexes are usual; the abdominal reflexes can rarely be obtained; plantar responses are absent or of the flexor type. Most commonly at this time the cranial nerves are normal, though trismus, facial weakness or strabismus may persist for a while. In the upper limbs, weakness and inco-ordination are more usual than complete paralysis. Return of function is not long delayed, and as power is regained spasticity may develop. Deformities of muscular origin, particularly in the lower limbs, and evidence of muscular inco-ordination may enlarge the clinical picture.

In the majority of instances, after a period of weeks or months according to the severity of the initial paralysis, recovery is almost complete, but in the spinal type some spastic weakness of the lower extremities may remain; moreover, muscular deformities of the limbs may recur later (*vide* Case 2).

Some sensory loss commonly accompanies the motor disturbances and may take the form of complete anæsthesia over the paralysed area, in certain cases affecting those parts of the body below the nipple level, or may be incomplete or dissociated. At the onset of nervous illness, hyperæsthesia may be detected just above the level of apparent maximal involvement of the cord, and pain, sometimes severe, may be experienced in the head, back or limbs. Pain may recur, especially in the extremities, immediately prior to return of motor function. The discrimination between hot and cold is usually regained last, but recovery from sensory disturbances precedes that from motor paralysis.

On the mental side, the duration of somnolence varies much from case to case (seven to fourteen days in our series). The return of speech may be delayed, and though clearly understanding remarks addressed to him the patient may for a time be unable to reply coherently. This dysarthria is probably due to imperfect co-ordination of muscles concerned in the act of talking. In our series this phenomenon was most marked

in Case 5, but it differed considerably in detail from the disturbances of speech described by the older writers. An emotional stage is quite common, but more striking mental derangement may be seen in the early days of convalescence. Delusions, abnormal behaviour and moral perversions are features of this phase, during which functional manifestations may be superimposed upon earlier organic lesions. In our experience this stage has been short-lived (*vide* Cases 4 and 5), and in none of the recovered cases has there been permanent mental abnormality.

These then are the symptoms of acute perivascular myelinoclasia, whether occurring in the course of smallpox, vaccinia or measles (Wohlwill, 1928; Greenfield, 1929). Greenfield concluded that "no clinical or pathological distinction can be drawn between the encephalomyelitis following measles, and that which may follow vaccination and smallpox"; and no one reading the remarks introductory to his clinical description can fail to agree that many of them would form an equally fitting preface to our own cases, while, as already stated, we have been unable to detect any histological differences between the cases following vaccination and the present series following smallpox.

Owing to their almost invariably favourable course, the nature of the nervous complications of varicella, rubella and mumps is less clear. Clinically, many of the cases arising after varicella have shown predominant affection of the cerebellum, and in the sole fatal case of this type examined histologically (van Bogaert, 1930), lesions, though more marked in the white than in the grey matter, do not appear to have been those of acute perivascular myelinoclasia. Zimmerman and Yannet (1931), however, in a child with fever, irritability and convulsions beginning three days after appearance of the rash, described diffuse non-characteristic degeneration of ganglion cells, and perivascular destruction of the myelin sheaths in the parietal and occipital white matter. The clinical features of the cases following rubella recorded by Bénard (1921) and Brock (1929) suggested acute perivascular myelinoclasia, but histological proof was lacking.

The position of the so-called paralytic accidents of antirabic treatment is also confused, since, as Hurst (1932) has pointed out, various observers have not always been at pains to distinguish two very different conditions. On the one hand there are cases of true street-rabies developing in spite of treatment, and rare cases where the *virus fixe* has proved pathogenic for man (França, 1910; Busson, 1926); on the other hand, the residuum are undoubtedly examples of acute perivascular

myelinoclasia. Bassoe and Grinker (1930) and Stuart and Krikorian (1930) have recently described such cases; the case of Fielder (1916) was certainly, and that of Babes and Mironesco (1908) probably, similar.

If, therefore, we find the same clinical and pathological condition following after a roughly similar "incubation period," such different predisposing causes as smallpox, measles, antirabic treatment, &c., the conclusion seems inevitable that we are dealing with an independent malady activated by the conditions mentioned, and not with one resultant upon some change in virulence or other property of the virus of the primary affection. In particular, it is difficult to envisage what modification of the virus of rabies, which always produces the polioclastic type of inflammation with major incidence upon the grey matter, destruction of nerve-cells and the development of characteristic inclusions, could make it responsible for an encephalopathy characterized by a primary destruction of the myelin sheaths and but little alteration in the nerve-cells which do not contain Negri bodies. Or, again, that the virus of vaccinia, which is not in the strict sense of the term neurotropic, but which gives rise to lesions primarily meningeal (Hurst and Fairbrother, 1930), can, after some hypothetical modification involving no change in its other pathogenic properties, produce lesions which from the neuropathological aspect are the very antithesis of those of "cerebral vaccinia."

But another, and to our minds still more weighty, objection to the theory of "direct causation" depends on the periodicity of these visitations of nervous disease. Acute perivascular myelinoclasia is no new malady and, judging by the numerous accounts published, cases following smallpox were relatively frequent in the closing decades of the nineteenth century; after Aldrich's paper in 1904, however, with the sole exception of Eichorst's case in 1913, no mention of the condition seems to have been made in the literature until McIntosh's note of 1928. Of course, during much of the present century smallpox was an uncommon disease in this country, but the same argument does not apply in the case of vaccinia. It seems likely that "post-vaccinal encephalitis" was first seen by Comby in 1907, and Turnbull and McIntosh's first case occurred in 1912, yet the recent outbreak is unprecedented. The fact that the condition has lately again become infrequent is fully in accordance with the known behaviour of acute perivascular myelinoclasia, and for this reason can certainly not be ascribed solely to the efforts, however soundly based, which have been aimed at the prevention of the condition.

Koritschoner and Schweinburg (1925), dealing with the statistics of antirabic inoculation at the Vienna Institute, state that between 1894 and 1914, 7,632 cases were treated without accident, while between 1915 and 1923, 6,764 cases showed 39 paralytic accidents. Greenfield (1929) stresses a similar periodicity in the case of the disease following measles, and of other encephalopathies presenting a somewhat similar histological picture, e.g., neuroptico-myelitis. Our own views are exactly expressed in the ensuing extract from his article: "A condition which occurs in so small a proportion of cases of measles, and which in one year may suddenly appear with much greater frequency and cause more deaths than in the previous twenty years, is unlikely to be due to a sudden change in the nature of so common a disease. It is much more likely to be due to some other concurrent epidemic which does not produce much obvious effect unless the carrier of the virus is attacked by smallpox or measles." We would merely emphasize the still greater improbability of a similar change in pathogenic properties occurring simultaneously in at least three different viruses, viz., those of smallpox, vaccinia and measles.

If, on the other hand, the virus of the exanthem plays merely an indirect rôle, it is possible that acute perivascular myelinolysis may from time to time occur as an independent disease. What evidence is there to support this?

Turnbull (1928) states that "there can be no doubt that a condition resembling post-vaccinal encephalitis has occurred independently of recent vaccination and observed exanthemata. Küssner and Brosin (1886) described accurately identical changes in the cord of a man who had suffered for a year from chronic gonorrhœa. The changes observed in the cord in the first case of Francotte (1890) appear to be similar, whilst Krabbe (1913) described the changes in the brain. Very similar but more chronic changes were described by Dreschfeld (1894). Wohwill (1928) said that he had observed changes identical with those of post-vaccinal encephalitis in a patient who was not suffering from any known infectious disease."

Greenfield (1930) recorded two cases identical with those following vaccination, &c., occurring after "influenza." In the second case, however, it seems highly probable that the influenzal symptoms represented merely the febrile onset of the nervous condition, a view with which McAlpine (1931) concurs.

During the last few years numerous observers have noted a general increase in the incidence of what is termed acute disseminated encephalo-

myelitis, and many clinical accounts have been published, e.g., those of Redlich (1927), Pette (1927), Martin (1928), Flatau (1929), Spiller (1929), van Bogaert and Baeten (1930), McAlpine (1931), &c. It is not certain that all these cases have belonged to the type of disease at present under discussion; but few pathological accounts are available, and while Paul (1928) thought the condition in his cases similar to that in "post-vaccinal encephalitis," Pette (1928), Cournand (1930) and Dagnélie and van Bogaert (1931) have described lesions more closely resembling those of "acute disseminated sclerosis," which condition we would prefer to designate "acute focal myelinoclasia." The cases of Brain, Hunter and Turnbull (1929) do not, either clinically or pathologically, tally entirely with either of these groups.

The work of Grinker and Bassoe (1931) makes it likely that we have to separate a number of closely-related but distinct morbid entities, for while their first case exhibited a histological picture identical with that of "post-vaccinal encephalitis," their second case resembled more closely the so-called "acute disseminated sclerosis," and their third case was again different from either. They state that if a pathological classification of infections of the central nervous system on the basis of distinct, regularly occurring microscopical changes were proposed, each group would embrace examples of more than one clinical syndrome. Excluding cases of syphilis, parasitic infections and sepsis, the distinguishing features of the various groups might be as follows:—

(1) Severe focal demyelination, less severe axonal change, microgliosis, mild or absent perivascular infiltration, gliosis—disseminated sclerosis and some cases of acute disseminated sclerosis.

(2) Focal incomplete or complete softenings, not perivascular, microgliosis, variable lymphocytic infiltration, vascular and connective-tissue proliferation—acute disseminated encephalo-myelitis and acute disseminated sclerosis.

(3) Focal incomplete perivascular softening involving the whole nerve-fibre, coalescence of lesions, microgliosis, mild lymphocytic reaction, secondary gliosis—post-vaccinal encephalitis, &c., and disseminated encephalo-myelitis.

(4) Diffuse subcortical destruction of nerve-fibres, probably primary in the myelin, mild or absent lymphocytic infiltration, primary progressive gliosis with secondary regressive glial forms, connective-tissue scar—Schilder's encephalitis and disseminated encephalo-myelitis.

(5) Diffuse but relatively selective ganglion-cell destruction, abundant perivascular and tissue lymphocytic reaction, mild micro-

gliosis, white matter spared—rabies, encephalitis lethargica and poliomyelitis.

(6) Hyperplastic meningeal reaction, regressive changes in capillary endothelium, formation of new blood-vessels, degenerative changes in nerve-cells, absent mesodermal infiltrations—toxic encephalitis in the acute infections, lead poisoning, &c.

It seems fair to conclude, therefore, that acute perivascular myelinolasis may occur independently of any exanthem, and is entitled to recognition as an independent clinical and pathological entity; the application of a single comprehensive term to all cases, whatever the predisposing malady, is the logical development of this knowledge. It is clear, moreover, that different authors have described as disseminated encephalo-myelitis rather widely differing pathological conditions, and until the present confusion regarding disseminated encephalo-myelitis, acute disseminated sclerosis, &c., has been dispelled, in the absence of any definite knowledge of their ætiology, it seems desirable to classify this group of obviously related diseases on a histological basis. For the time being, then, nomenclature will depend on distinctive histological features, and this principle has been followed in the present paper.

Finally, whatever the exact relationship between acute perivascular myelinolasis and acute focal myelinolasis, and between the latter and disseminated sclerosis, these diseases are in certain features sufficiently similar to suggest the wisdom of considering the ætiology of the group rather than that of the individual malady.

In the case of acute perivascular myelinolasis the discovery of a filterable virus has been eagerly awaited. The grouping of cases in certain districts, the occasional affliction of more than one member of a family,¹ the periodicity of the disease, the febrile onset of symptoms, suggest an infectious origin, yet it must be remembered that such evidence is not necessarily conclusive and that other factors may recur at intervals and affect only a certain proportion of individuals; as a rather remote analogy we might quote the outbreaks of lathyrism in India.

Experimental work has told us very little, and that only of a negative character. All our own attempts to reproduce the condition by intracerebral inoculation, combined on occasion with skin vaccination, of

¹ The case of dissimilar twins who, vaccinated on the same day, both developed "post-vaccinal encephalitis" and died on successive days recently attracted considerable notice in Parliament and in the press. Histological examination was performed by one of us. (E.W.H.).

monkeys and rabbits with brain emulsions from cases following vaccinia and smallpox have been fruitless, as have those of other workers. Cournand obtained similar negative results in monkeys and rabbits with the brains of two of his spontaneous cases showing the focal type of lesions ("acute disseminated sclerosis"), while the "spherula insularis" as the causative organism of disseminated sclerosis is now generally discredited. Although as a rare event vaccine virus has been isolated from the brains of the post-vaccinal cases, this observation has no ætiological significance, as general dissemination of the virus normally follows vaccination; it has already been stated that the lesions produced in the nervous system by the vaccine virus are totally different from those of acute perivascular myelinoclasia.

Though perhaps of little import, it is a fact that in all the (now numerous) neurotropic virus diseases of man and animals, the brains exhibit what Schroeder (1925) has called the polioclastic type of inflammation, that is to say, that the primary attack is on the grey matter, while of the myelinoclastic diseases characterized by a primary affection of the myelin sheaths, not one has yet been shown to result from the action of a virus. While the long-disputed question as to whether the lesions of disseminated sclerosis are primarily inflammatory or not has, apparently, recently almost always been answered in the positive, we do not believe that this conclusion necessarily follows from the evidence available. In the purely degenerative lesion resulting from the aseptic occlusion of a cerebral blood-vessel, the products of nervous disintegration may excite very lively inflammatory phenomena. Some of the disintegration products of myelin, and in particular cholesterol, are powerful tissue irritants, and the variable inflammatory manifestations in acute perivascular myelinoclasia could conceivably be explained as due to their action. Further, the demyelination in acute perivascular myelinoclasia apparently occurs suddenly and with great rapidity, and in cases fatal some time from the onset there is no indication that after the first few hours the lesions progress; this would probably be in keeping more with a sudden attack on the myelin sheath by a toxin or enzyme than with that of a living organism. There is, of course, the possibility that the condition is the result of an infection, but that the nervous changes are conditioned by some product of that infection and are not due to a direct attack of the infective agent itself.

It is of interest that in disseminated sclerosis Brickner (1930, 1931) has obtained evidence that the blood-serum shows myelin-destroying properties not possessed by normal serum. His results were not due to an

excessive amount of normal lipase or to decreased anti-lipase activity, as tests indicated a difference in properties between the normal lipolytic agent and that of disseminated sclerosis. In our own experiments, using an active preparation of pancreatic lipase, we demonstrated that *in vitro* the amount of acid produced after incubation with brain-emulsion was roughly the mean of that produced by the same preparation using olive-oil as substrate on the one hand, and ethyl butyrate as substrate on the other. But on intracerebral or intrathecal inoculation no lesions analogous to those of any of the demyelinating diseases developed: intravenous inoculation into monkeys suffering from poliomyelitis or cerebral vaccinia, in which it might reasonably be supposed that vascular and meningeal permeability was greater than normal, was also ineffective. It must, of course, be remembered that a lipase, or rather an esterase, has been demonstrated in small amounts in normal nervous tissues (Quinan, 1916), and, presumably, must be kept in check by anti-lipase activity. It is just conceivable that local removal of the inhibitory factor might result in demyelination in the area concerned.

While these concluding remarks are purely speculative, in the absence of fact speculation may promote an unbiased approach to a problem and lead to solution along what appear at first improbable lines. If, as appears likely, the demyelinating maladies we have mentioned are aetiologicaly more or less closely related, it would seem that acute perivascular myelinocalasis, as the most acute representative of the group, would offer the most favourable field for research.

CONCLUSIONS.

Acute perivascular myelinocalasis is a definite clinical and pathological entity with a more or less characteristic symptomatology and a highly characteristic histology.

It may occur independently of any recognized exciting factor, or it may follow certain exanthemata, smallpox, vaccinia, measles, varicella, and probably rubella. It may also occur during the course of antirabic treatment.

The aetiology is unknown but may be connected with that of acute focal myelinocalasis ("acute disseminated encephalo-myelitis," "acute disseminated sclerosis") and of disseminated sclerosis.

REFERENCES.

- ALDRICH, C. J. (1904). *Amer. Journ. Med. Sci.*, **127**, 198.
AUCHÉ and HOBBS (1894). *C.R. Soc. Biol.*, **46**, 703.
BABES, V. and MIRONESCU, T. (1908). *Ibid.*, **64**, 964.
BASSON, P. and GRINKER, R. R. (1930). *Arch. Neurol. Psychiatr.*, **23**, 1138.

- BÉNARD, R. (1921). *Bull. Mém. Soc. méd. d. Hôp. Paris*, **45**, 1448.
- BERNHARDT, M. (1871). *Berl. klin. Wschr.*, **8**, 561.
- BRAIN, W. R. (1928). *Proc. Roy. Soc. Med.*, **22**, 1174.
- BRAIN, W. R., HUNTER, D. and TURNBULL, H. M. (1929). *Lancet*, (i), 221.
- BRICKNER, R. M. (1930). *Arch. Neurol. Psychiatr.*, **23**, 715.
- Idem.* (1931). *Bull. Neurol. Inst.*, New York, **1**, 105.
- BROCK, J. H. E. (1929). *Lancet* (ii), 1190.
- BUSSON, B. (1926). *Centralbl. f. Bakt., Orig*, **99**, 80.
- CLIFTON, F. (1724). "Dissertatio medica inauguralis de distinctis et confluentibus variolis," Leyden.
- COMBENALE, F. (1892). *Arch. gén. de Méd.*, **169**, 641.
- COMBY, J. (1907). *Arch. d. méd. d. enf.*, **10**, 598.
- COURNAND, A. (1930). "La Sclérose en Plaques aiguës," Paris.
- DAGNÉLIE, J. and VAN BOGAERT, L. (1931). *Rev. neurol.* (i), 576.
- DAMASCHINO (1871). *Gas. méd. de Paris*, **26**, 505.
- DRESCHFELD, J. (1894). *Brit. Med. Journ.* (i), 1174.
- EICHORST, H. (1918). *Deut. Arch. f. klin. Med.*, **111**, 1.
- FIELDER, F. S. (1916). *Journ. Amer. Med. Assoc.*, **66**, 1769.
- FISSINGER (1898). *Méd. mod.*, **9**, 841.
- FLATAU, E. (1929). *L'encéphale*, **24**, 619.
- FRANÇA, O. (1910). *Centralbl. f. Bakt., Orig.*, **55**, 154.
- FRANCOTTE, Z. (1890). *Arch. d. Neurol.*, **20**, 46.
- FREIND, J. (1780). "Nine Commentaries upon Fevers and two Epistles concerning the Small-Pox," London.
- GREENFIELD, J. G. (1929). *Brain*, **52**, 171.
- Idem.* (1930). *Journ. Path. Bact.*, **33**, 458.
- GRINKER, R. R. and BASSOE, P. (1931). *Arch. Neurol. Psychiatr.*, **25**, 728.
- GRUNBERG (1930). *Klin. Wschr.*, **9**, 1127.
- GUBLER and LABORDE (1871). *Gas. d. Hôp.*, **21**, 829.
- GUTTSTADT (1872). *Deut. Klinik.*, **24**, 847.
- HEKMAN, J. (1930). *Bull. Acad. Méd.*, **103**, 589.
- HORDER, T. (1929). *Lancet*, (i), 1301.
- HURST, E. W. (1932). *Journ. Hyg.*, **32**, 88.
- HURST, E. W. and FAIRBROTHER, R. W. (1930). *Journ. Path. Bact.*, **33**, 463.
- IMMERMAN, H. (1902). Nothnagel's Encyclopædia of Practical Medicine, English Translation, Philadelphia and London.
- KLEINBERGER, C. (1913). *Arch. f. Psychiatr.*, **50**, 632.
- KORITSCHONER, R. and SCHWEINBURG, F. (1926). *Zeit. f. Immunitätsf.*, **42**, 217.
- KRABBE, K. H. (1913). *Zeit. f. d. ges. Neurol. u. Psychiatr.*, **20**, 108.
- KÜSSNER, B. and BROSI, F. (1886). *Arch. f. Psychiatr.*, **17**, 239.
- LEROY D'ÉTIOLLES, R. (1856). "Des paralysies des membres inférieurs," Paris.
- LOWENBERG, H. and SHALLER, A. L. (1926). *Arch. Pediatr.*, **43**, 78.
- MACCOMBIE, J. (1905). In Allbutt and Rolleston's "System of Medicine," London.
- MCALPINE, D. (1931). *Lancet* (i), 846.
- MCINTOSH, J. (1928). *Brit. Med. Journ.* (ii), 334.
- MCINTOSH, J. and SCARFF, R. W. (1928). *Proc. Roy. Soc. Med.*, **21**, 705.
- MARTIN, J. P. (1928). *Lancet* (ii), 628.
- OETTINGER and MARINESCO, G. (1895). *Sem. méd.*, **15**, 45.
- PAUL, F. (1928). *Méd. Klinik.*, **24**, 732 and 778.
- PETTE, H. (1927). *Munch. med. Wschr.*, **74**, 1409.
- Idem.* (1928). *Deut. Zeit. f. Nervenheilk.*, **105**, 76.
- QUINAN, C. (1916). *Journ. Med. Res.*, **35**, 79.
- REDLICH, E. (1927). *Wien. klin. Wschr.*, **40**, 344.
- REPORTS OF THE VACCINATION COMMITTEE (1928), (1931). H.M. Stationery Office.
- RUNDLE, O. (1929). In Ker's "Infectious Diseases," London.
- SCHAMBERG, J. F. and KOLMER, J. A. (1928). "Acute Infectious Diseases," Philadelphia.

- SCHRODER, P. (1925). *Deut. med. Wschr.*, **51**, 973.
SOTTAS, M. (1892). *Gas. d. Hôp.*, **65**, 405.
SPILLER, W. G. (1908). *Brain*, **26**, 424.
Idem. (1929). *Arch. Neurol. Psychiatr.*, **22**, 647.
STUART, G. and KRIKORIAN, K. S. (1980). *Lancet* (**i**), 1128.
TROUP, A. G. and HURST, E. W. (1980). *Lancet* (**i**), 566.
TURNBULL, H. M. (1928). *Brit. Med. Journ.* (**ii**), 881.
TURNBULL, H. M. and MCINTOSH, J. (1926). *Brit. Journ. Exp. Path.*, **7**, 181.
VAN BOGAERT, L. (1980). *Journ. Neurol. Psychiatr.*, **30**, 623.
VAN BOGAERT, L. and BAETEN, J. (1980). *Presse med.* (**ii**), 1770.
WAGNER (1872). *Arch. d. Heilk.*, **13**, 107.
WESTPHAL, C. (1872). *Arch. f. Psych. u. Nerv.*, **3**, 376.
Idem. (1874). *Ibid.*, **4**, 388.
WHIPHAM, T. and MYERS, A. T. (1886). *Trans. Clin. Soc., London*, **19**, 164.
WOHLRAB, A. (1872). *Arch. d. Heilk.*, **13**, 512.
WOHLWILL, F. (1928). *Zeit. f. d. ges. Neurol. u. Psychiatr.*, **112**, 20.
ZIMMERMAN, H. M. and YANNET, H. (1931). *Arch. Neurol. Psychiatr.*, **26**, 322.
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A NOTE ON THE RESULT WHICH FOLLOWS THE GRAFTING OF THE RAW PERIPHERAL END OF THE DIVIDED CERVICAL SYMPATHETIC NERVE TO ANOTHER NERVE IN THE VICINITY.¹

BY ARTHUR B. DUEL, NEW YORK, AND SIR CHARLES BALLANCE.

DURING the progress of a research designed to determine the effect of anastomosing the central end of the divided cervical sympathetic nerve to the peripheral end of certain divided motor nerves of the neck, the opportunity arose of observing the results which follow:—

(a) The anastomosis of the peripheral end of the divided cervical sympathetic to some other neighbouring nerve.

(b) The leaving of the peripheral end of the divided cervical sympathetic nerve without surgical union with any other nerve.

The prominent signs caused by division of the cervical sympathetic nerve in the cat are, enophthalmos, small pupil, prominence of the nictitating membrane, and drooping of the whisker hairs. All these signs and symptoms disappear on Faradic stimulation of the peripheral end of the divided cervical sympathetic nerve. Other signs, as the dilatation of the arteries of the pinna and the absence of sweating of the skin of the face on the side of operation, were ignored. It was thought that the four signs chosen for observation would suffice to indicate by their disappearance, or by their persistence, the recovery or lack of recovery of the ocular signs caused by section of the cervical sympathetic.

The operations were made on 46 cats and 2 Rhesus monkeys. A few of the cats died of some known or unknown malady, a few were killed by chloroform, and a few have been too recently operated on for a judgment to be reached as to the final condition of their ocular signs. A sufficient number—28—of the experimental animals remain for a definite conclusion to be formed as to the value of suturing the peripheral end of the divided cervical sympathetic nerve to another nerve.

It is known that in man, when the cervical sympathetic has been

¹ The research on which this paper is founded is much indebted to the generous support of the Carnegie Corporation, of the Milbank Memorial Foundation, of the Lillian Babbitt Hyde Foundation, and of several private friends.

severed, occasionally after a more or less long time the ocular signs disappear. It may be presumed that in such a case the raw peripheral end of the sympathetic becomes adherent to, and later is in functional union with, some neighbouring nerve. It is not possible to ascertain the percentage of recoveries in man. The conditions for which in surgery the cervical sympathetic is divided are so serious (cardiac pain, Raynaud's disease, &c.) that the surgeon's mind is concentrated on the relief given to the serious symptoms from which the patient is suffering, and the ocular signs in comparison seem to be but a trivial incident in the case.

We were not altogether surprised at the results of our experiments. Langley and Anderson [4], in 1904, anastomosed the central end of the 5th cervical nerve to the peripheral end of the cervical sympathetic nerve. The effects of stimulation of the 5th cervical nerve some time later showed clearly that functional union had taken place, for all the normal effects of stimulation of the cervical sympathetic nerve were observed.

One of us (B) [1] performed an experiment on a cat (August, 1927), which confirmed and extended the results obtained by Langley. The central end of the divided cervico-facial division of the facial nerve was united to the peripheral end of the divided cervical sympathetic nerve. At the end of six months there was no enophthalmos, and no prominence of the nictitating membrane; the pupil was not small, but was not quite so large as the opposite or normal pupil, and the whisker hairs on the side of the operation no longer drooped, but stood out like those of the opposite side.

Cannon [2] united the phrenic nerve in cats low down in the neck to the cervical sympathetic. Rhythmic efferent impulses associated with respiration passed along the sympathetic, presumably to the thyroid, and provoked excitability, rapid pulse, increased metabolism and other symptoms which were interpreted as evidence of experimental hyperthyroidism. Horrax [3] repeated these experiments and confirmed Cannon's conclusions.

SYLLABUS OF EXPERIMENTS.

A. The main operation was cervical sympathetic-hypoglossal anastomosis (right side).

The secondary operation was hypoglossal-cervical sympathetic anastomosis (right side).

1. CAT.—226 days. No enophthalmos, pupils equal, whiskers of both sides at same level. Right nictitating membrane shows slightly.

2. *CAT*.—No secondary anastomosis performed.

86 days. All signs of cervical sympathetic division well marked.

Cat anæsthetized.—Faradism: electrode was placed on the skin $\frac{1}{4}$ in. behind and above the right angle of mouth—the eyeball advanced, the pupil enlarged and the nictitating membrane disappeared. The Faradism at this spot was continued for some little time with interruptions. It was then noted that the stimulation caused both pupils to enlarge at the same time.

When the cat had recovered from the ether anæsthesia there was no difference between the eyes; the ocular signs on the right side had disappeared. Three and a half months later complete recovery of the right ocular signs was maintained.

The explanation seems to be that at the time of Faradic stimulation, 86 days after the severance of the cervical sympathetic, its peripheral end had become grafted on to another neighbouring nerve, and that the Faradism overcame the obstruction at the point of anastomosis which had up to the moment of Faradism prevented the passage of nerve impulses.

3. *CAT*.—70 days. No difference between the eyes. Two months later same report.

4. *CAT*.—70 days. No difference between the eyes.

5. *CAT*.—No secondary anastomosis performed.

323 days. No recovery of the ocular signs, but perhaps they are not so noticeable as at first.

6. *CAT*.—No secondary anastomosis performed.

178 days. No change whatever in the ocular signs.

7. *RHESUS MONKEY*. No secondary anastomosis performed.

180 days. No change in the ocular signs.

B. The main operation was cervical sympathetic-facial anastomosis (right side). In the experiments no secondary anastomosis was done.

8. *CAT*.—No secondary operation performed.

Death on the thirty-fifth day. No change in the ocular signs.

9. *CAT*.—No secondary anastomosis performed.

51 days. On placing the electrode above and behind angle of mouth: eyeball moved forwards, pupil dilated, membrana nictitans disappeared.

These were only temporary results of the stimulation. The ocular signs were as marked after the stimulation as before. Four months later there was no amelioration of the ocular signs.

10. *CAT*.—No secondary anastomosis performed.

70 days. Ocular signs typical.

11. *CAT*.—No secondary anastomosis performed.
172 days. There is no enophthalmos, the right eyeball is more prominent than the left, but the right pupil is small, the nictitating membrane prominent and the whiskers droop. Presumably the fibres in the peripheral end of the divided cervical sympathetic which innervate the muscle of Müller have become functionally attached to some other nerve, but why there is exophthalmos cannot be explained so easily.
 12. *CAT*.—No secondary anastomosis performed.
231 days. Ocular signs entirely unchanged.
 13. *CAT*.—No secondary anastomosis performed.
230 days. Ocular signs quite unchanged.
 14. *RHESUS MONKEY*.—No secondary anastomosis performed.
125 days. Ocular signs present but seem to be less noticeable than formerly.
- C. The main operation was cervical sympathetic-superior laryngeal anastomosis (right side).
The secondary anastomosis was superior laryngeal-cervical sympathetic anastomosis (right side).
15. *CAT*.—30 days. No change in the ocular signs.
 16. *CAT*.—155 days. Complete recovery—both eyes entirely alike.
- D. The main operation was anastomosis of the cervical sympathetic with the motor portion of superior laryngeal nerve (right side).
The secondary operation was anastomosis of the motor portion of superior laryngeal nerve with the cervical sympathetic (right side).
17. *CAT*.—100 days. Pupils equal; no enophthalmos; membrana nictitans still shows a little.
 18. *CAT*.—In this experiment the secondary operation was hypoglossal-cervical sympathetic side-to-end anastomosis. This was found more convenient than using the central end of the motor part of the superior laryngeal nerve which is a very small nerve.
Notes made on 96th day and 226th day: ocular signs completely disappeared.
 19. *CAT*.—155 days. No difference between the two eyes. The secondary anastomosis in this experiment was of the superior laryngeal nerve, with the cervical sympathetic, side to end.
- E. The main operation was cervical sympathetic, descendens noni anastomosis (right side).
The secondary operation was descendens noni, cervical sympathetic anastomosis (right side).
20. *CAT*.—196 days. Both eyes alike. Ocular signs completely disappeared.

- F. The main operation was cervical sympathetic, phrenic anastomosis.
The secondary operation consisted of grafting the peripheral end of the cervical sympathetic to (a) the central end of the phrenic end to end, or (b) to the anterior primary division of the 5th cervical nerve, end to side (right side).
21. *CAT*.—The secondary anastomosis consisted of the grafting of the peripheral end of the cervical sympathetic on to the 5th cervical nerve. 168 days. Pupils equal; no enophthalmos; whiskers at same level on both sides; slight appearance of membrana nictitans.
22. *CAT*.—The secondary anastomosis consisted of the grafting of the peripheral end of the cervical sympathetic to the phrenic nerve, end to end. 172 days. Same result as in Cat 21.
- G. The main operation was cervical sympathetic-recurrent laryngeal anastomosis.
The secondary anastomosis, the peripheral end of the cervical sympathetic was never grafted to the proximal end of the recurrent laryngeal.
23. *CAT*.—The secondary anastomosis was an end to side grafting of the peripheral end of the cervical sympathetic to the lower border of the hypoglossal. 60 days. No enophthalmos; other ocular signs have nearly disappeared.
24. *CAT*.—The secondary anastomosis was an end-to-side union of the peripheral end of the cervical sympathetic to the lower border of the superior laryngeal nerve. 53 days. Same result as in Cat 23.
25. *CAT*.—No secondary anastomosis.
90 days. No improvement in the ocular signs.
26. *CAT*.—No secondary anastomosis.
156 days. No improvement in the ocular signs whatever.
- H. The main operation was cervical sympathetic-glossopharyngeal anastomosis. The whole glossopharyngeal or only its motor part was used in the experiment (right side).
No secondary anastomosis was carried out in either of the two experiments performed.
27. *CAT*.—The notes on the 95th and 231st days state that there is no improvement in the ocular signs.
28. *CAT*.—Died under ether on the 32nd day. There was no change in the ocular signs.

ANALYSIS OF EXPERIMENTS.

The experiments were performed on Cats and Rhesus Monkeys.

(A) The peripheral end of the divided cervical sympathetic was grafted to:—

- (1) The central end of the divided hypoglossal, end to end, or to the side of the hypoglossal, end to side.

- (2) The central end of the divided superior laryngeal, end to end, or to the lower border of the superior laryngeal, end to side.
- (3) The central end of the divided motor portion of the superior laryngeal, end to end.
- (4) The central end of the divided descendens noni, end to end.
- (5) The central end of the divided phrenic, end to end.
- (6) The anterior primary division of the 5th cervical nerve, end to side.

The animals remained alive from 30 to 226 days after the experiments were done. In all the 13 experiments the ocular signs disappeared except in three animals in which death occurred at an early stage of the experiment. Great improvement of the ocular signs was observed 60 days after the operation, and in 100 to 120 days little difference, if any, could be seen in comparing the two eyes. Perhaps a quicker recovery occurred when the peripheral cervical sympathetic was united to the proximal hypoglossal, the proximal phrenic or to the side of the 5th cervical nerve than when anastomosed to other nerves.

(B) In 15 experiments the peripheral end of the cervical sympathetic was left ungrafted to another nerve. The animals remained alive after the experiments for from 32 to 323 days. With the exception of two cats no change in the ocular signs was noted. In Experiment 2 the ocular signs were apparently cured on the 86th day by Faradism. In Experiment 11 slight exophthalmos was observed on the 172nd day, but the other ocular signs due to division of the sympathetic showed no change.

Remarks.—The whisker hairs did not seem always to droop, or else the drooping was so slight that it was not observed. The disappearance of the drooping of the whisker hairs was the first hint that recovery was taking place. The recovery of the ocular signs was first shown by the advancement of the eyeball so that enophthalmos was no longer present. The improvement in the size of the pupil and its reactions so that it became in all respects comparable to the opposite or normal pupil took a much longer time. The last sign to disappear was the prominence of the membrana nictitans. Even when there was no evidence of other ocular signs a slight indication of the membrana nictitans sometimes remained at the inner canthus.

REFERENCES.

- [1] BALLANCE. "Anastomosis of Nerves," *Arch. of Neurol. and Psychiat.*, 1931, **25**, 1.
- [2] CANNON, W. B., BINGER, C. A. L., and FITZ, R. *Amer. Journ. of Physiol.*, 1914-15, **36**, 365.
- [3] HORRAX, G. See "Studies in Intracranial Physiology and Surgery by Harvey Cushing." Oxford University Press. Footnote to pp. 75-76.
- [4] LANGLEY and ANDERSON. *Journ. of Physiol.*, 1904, **30**, 439.

THE INFLUENCE OF SECTION OF THE VESTIBULAR NERVE ON THE SINGLE-SHOCK REFLEX FLEXOR RESPONSE.

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IN a recent communication, Fulton, Liddell and Rioch described the influence upon the knee-jerk of unilateral destruction of the vestibular nuclei and of the eighth nerve [7]. They found an increased susceptibility to inhibition of the knee-jerk, together with a diminution in the postural reflexes of the same side. The behaviour of a flexor muscle under the same conditions presented itself as an obvious sequel for investigation.

We have examined and now offer an account of a brief series of similar lesions in relation to the reflex responses to single-shock stimuli of a flexor muscle, *tibialis anticus*.

METHOD.

Making the lesion.—The animals used were cats. Under deep anæsthesia with pure ether and with full aseptic technique, the occipital ridge was exposed and a trephine opening made just caudal to the ridge and some way lateral. The dura was opened and the subjacent cerebellar tissue gently retracted in a medial direction. Very little retraction exposed the eighth nerve at the bottom of the wound. The nerve was then severed with a small hooked knife. A smart brief hæmorrhage denoted severance of the accompanying artery. After hæmostasis, the wound was closed aseptically. Recovery was uneventful, except for the usual movements of spontaneous forced rolling. These could be so violent that asepsis of the skin-wound was endangered and so it became our custom to proceed with recording after only a few days' delay. During this time there was hypotonia on the side on which the eighth nerve was severed. Our preparations were, therefore, examined the first week after section of the labyrinthine nerve, during the stage of recovery when those symptoms are most in evidence which are ascribed to "irritation" (an unhappily vague term, discussed later in this paper).

In one preparation, the rubrospinal tract was divided by a stab in the floor of the fourth ventricle.

RECORDING.

Decerebration at mid-collicular level was performed under deep anæsthesia and the customary dissection made for myographic examination, viz., immobilization by nerve or tendon resection of all muscles of the hind limb except the two used for myographic examination, the left and right tibialis anticus, so that the limbs of the operated and unoperated side could, each in turn, be examined myographically by changing the position of the preparation in relation to the myograph. The popliteal nerve on each side was prepared for stimulation by Sherrington's glass-shielded electrode. The stimulating apparatus consisted of a students' coil (coreless) fed by a 2-v. accumulator. The primary coil was in series with a resistance box (P.O.) and the break key of a Lucas pendulum. The secondary coil was set at zero. The myograph was a frictionless optical model. The initial tension on the tendon was 60 grm. and observation was made on the strength of stimulus needed to elicit a barely visible reflex twitch of 3-grm. active tension and one of 170 grm. tension, the muscle shortening 1 mm. for 200 grm.

RESULTS.

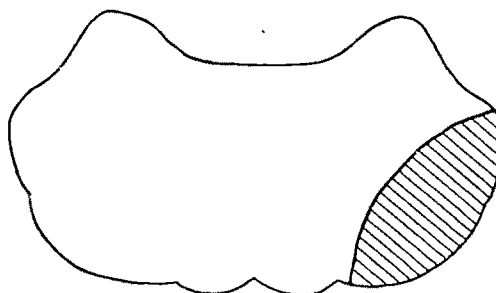
We found a difference between the reflex excitabilities of the motor centres on the two sides. On the side opposite the lesion, that is, on the side which, as many observers have noted, is clinically hypertonic, we

Days after section of 8th nerve	Ohms in primary for a 170-grm. break-shock reflex. (Average of decerebrate with both vestibular nerves intact, from another series of experiments, 40: values below 40 commonest)		Ohms in primary for 8-grm. break-shock reflex. (Average with both vestibular nerves intact 880: values below 250 commonest)	
	Same side as section	Opposite side	Same side	Opposite side
6	185	310	245	1,080
Same day	55	100	240	770
1 (Partial section; ataxy without forced rolling)	105	250	220	360
1	—	190 90	—	370 280
2	5	5	160	850
1 (Both sides operated)	80-40		810-325	
1 (Almost complete)	870	40	1,580	500

found an increased excitability of the flexor's reflex centre. On the side on which the vestibular nerve was cut, that is, on the hypotonic side, the threshold of stimulus needed was as a rule rather lower than normal but was less low than on the unoperated side.

Our results can be set out in a table (see above).

The first five experiments are in accord with fairly close correspondence in values for the 3-grm. twitch. It is interesting to note the difference in the last experiment, in which an unidentified portion of the nerve remained intact. In another animal in which the rubrospinal and neighbouring tracts had been divided seventeen days previously by sectioning a wedged-shaped area in the pons just headward of the emergence of eighth nerve (see figure) the values were:—



	Ohms for 170-grm. reflex twitch		For 8-grm. twitch	
	Same side as section	Opposite	Same side	Opposite
	17	120	310	515
After complete section of the cord	75	470	190	590

This preparation, therefore, reacted in the same way as the majority of vestibular preparations.

DISCUSSION.

The importance of the contribution from the vestibular nuclei for maintaining decerebrate rigidity is well established. If these nuclei or the tracts carrying their impulses are injured or ablated, rigidity very largely disappears, that is, hypertonus in extensor muscles is replaced by almost complete flaccidity in all muscles and the reactions of the preparations become "spinal" [7]. (The knee-jerk is then more easily inhibited by external stimuli [2] and "pale" rapid muscle is in abeyance [4].) These effects on extensors are ipsilateral and unilateral. *A priori* some change in the antagonists of the extensors might be expected and that on the same side. Our series, however, show less

increase in excitability of the ipsilateral than of the contralateral flexor. The contralateral increase may be due to a change in the intensity or extensity ("fringe") [5] of the subliminal excitation which is streaming down the long paths from the undamaged vestibular apparatus. On the other hand, there may be a decrease in inhibition such as occurs when the spinal cord or certain tracts within it are severed [13, 14]. This latter view is supported by the evidence presented in the accompanying paper that section of the lateral, medial, ventral reticulospinal tracts and of the vestibulospinal tract in the spinal cord releases the flexor centre from inhibition and makes it more easily excited [9]. But we have, in fact, no accurate evidence of the precise method by which the hyperexcitability on the contralateral side is brought to pass. That there is normally some sort of balance of function between the two labyrinths has long been believed. The crossed vestibular root which crosses the midline to the medial and lateral vestibular nuclei of the opposite side is probably an important path in correlating the functional activity of one labyrinth with that of the other. By its agency, one labyrinth can interact with the other either to increase excitability or decrease inhibition, or to effect both these results. Of descending tracts which pass down the cord on the side opposite their origin, there are the crossed vestibulospinal tract which arises from the descending vestibular nucleus of the opposite side and fibres in the medial longitudinal fasciculus from the medial vestibular nucleus of the opposite side. Part of the medial reticulospinal tract originates on the crossed side. The ventral reticulospinal tract has a crossed origin. The lateral reticulospinal tract has a crossed origin, but no close association with vestibular nuclei [8, 11, 12]. Therefore there exists at the level of both the first and second order neurones a possible basis for the effect we have described.

That extensor muscles of the side opposite the vestibular lesion show increased excitability is well known and evident enough before decerebration. We now record an increased excitability in the corresponding flexor centre. On the homolateral side, however, extensors are depressed and flexors but little affected. We conclude, therefore, that section of the vestibular nerve on one side changes the pattern of reflex response from that which obtains in the customary "intercollicular" preparation. Thus, although our wording is, of set purpose, different, we support the conclusion reached by Camis, "labyrinthectomy alters the normal reciprocal activity of, e.g., flexor and extensor muscles of the leg" [3]. A conclusion in such words unjustifiably suggests a modification of the

principle of reciprocal innervation, as Creed has pointed out, for the results may be due, in part, to the use of a "mixed" afferent nerve and cannot be ascribed entirely to labyrinthectomy. Our results may also be due, in part, to the same cause, since the popliteal nerve, so far as tibialis anticus is concerned, contains inhibitory as well as excitatory fibres [6]. Rather should it be said that labyrinthectomy alters the balance of the reflex background upon which the mixed afferent is brought to play. So the appearance of the resulting action is altered, although each component of the "mixed" nerve presumably continues to act reciprocally (though oppositely) on the flexor and extensor motor neurone. It must further be remembered that the non-auditory part of the eighth nerve itself is probably a "mixed afferent," since there is considerable evidence that the labyrinth is composed of a number of distinct but correlated functional entities [10]. By section of the labyrinthine nerve we have therefore deprived a reflex mechanism of a stream of impulses of varying import and then have brought to bear from the outside stimulation by a "mixed" afferent nerve. The increased excitability of the contralateral flexor which we find to be the consequence points either to a decreased inhibition or an increased excitation for its probable cause, or both.

In regard to the first possibility it is known that section or partial section of the spinal cord brings about lowering of the flexor threshold, which strongly suggests "release" from the inhibition of higher centres [13, 14]. On the other hand, the clinical state of the animals in the present experiments, with spontaneous rolling movements and contralateral hypertonia, tempts us to suggest that the origin of this increased excitability is the labyrinthine mechanism on the uninjured side, now no longer "balanced" against or inhibited by its fellow of the other side. In other words, our experimental procedure has not removed a direct inhibition but has upset a pre-existing balance of inhibition and produced excitation. If such an hypothesis be adopted, it need not negative the possibility that release of flexor centres by spinal section implies the cessation of higher *inhibitory* influence, for both inhibition and excitation from medullary and higher centres operate by long paths upon the lower spinal centres and the spinal paths subserving each process need not lie in the same anatomical region of the cord, any more than their centres of origin need be contiguous in the medulla. The belief that the lowered threshold of flexors is brought about by at least two processes receives support from study of the figures after complete spinal section in ordinary decerebrate preparations given in the accom-

panying paper [9]. In them, the threshold of the flexor centre is considerably lower than that resulting from section of the contralateral labyrinthine nerve, that is to say, the maximum degree of release is not achieved only by section of the labyrinthine nerve, but further release is possible by section of some spinal tract such as the reticulo-spinal. In our present brief series of experiments, it has not been possible to test this hypothesis by a search for further lowering of threshold from such a cause.

It is possible that injury of the vestibular nucleus, as opposed to section of the eighth nerve, might have had for the flexor a different result, as was noted for the extensor by Fulton, Liddell and Rioch. Spiegel [15] has observed that some factor or locus is concerned in the maintenance of decerebrate rigidity in addition to the vestibular nuclei. He has suggested the reticular substance of the medulla. In our own results with the flexor, the increase from vestibular section of contralateral excitability falls short of the increase produced by spinal section. It seems likely therefore, that for the flexor as for the extensor there is some factor in addition to the vestibular apparatus for "release" of the former.

The relation between this hyperexcitability of contralateral flexors and extensors is probably a close one. It is well known that some days after total unilateral labyrinthectomy, the forced movements cease to be spontaneous but can be elicited by rotation of the animal's snout. It remains, therefore, to inquire whether the excitability of the spinal centres, as revealed by our experiments, decreases *pari passu* with the reduction of forced movements. Such an investigation might also throw light on the cause of origin of these movements, whether due to permanent functional deprivation or to transient operative "irritation." The processes underlying the stage "irritation," to which have been ascribed the earlier signs such as forced rolling, are difficult to define. Nerve injury currents cannot play any part since they subside in a few minutes or hours and do not endure for days [1]. Inflammation due to sepsis is not there. Oedema only seems more possible. But in our opinion the early stage may well be due to acute lack of compensation following the functional removal of one labyrinth. The later stage, ensuing after a week or two, which has been called the "deficiency" stage, is due certainly to deficiency, combined probably with some degree of compensation, and following disuse or inhibition of previously active nerve-paths, or it may be due on the other hand to the activation of previously less active paths.

SUMMARY.

In cats the hypertonia which occurs in the opposite side during the first week or two after experimental severance of the eighth cranial nerve is accompanied by an increase in excitability of the spinal centres of tibialis anticus, a flexor muscle. There is a slight lowering of threshold also in the ipsilateral flexor centre. It is pointed out in discussion that this increased excitability, with its well-known clinical accompaniment of spontaneous rolling movements and of hypertonia, may be due directly to deprivation of the opposite labyrinth, and though less in degree, is comparable to the lower reflex threshold of flexor centres brought about by spinal section. But tentatively we hold to the hypothesis that it results from overaction of the intact ipsilateral labyrinth, now no longer "balanced" or inhibited by its fellow labyrinth.

REFERENCES.

- [1] ADRIAN, E. D. (1930). "The Effects of Injury on Mammalian Nerve-fibres," *Proc. Roy. Soc.*, **106B**, 596.
- [2] BALLIF, L., FULTON, J. F., LIDDELL, E. G. T. (1925). "Observations on Spinal and Decerebrate Knee-jerks with Special Reference to their Inhibition by Single Break-shocks," *ibid.*, **98B**, 589.
- [3] CANIS, M. (1930). "Physiology of the Vestibular Apparatus." Trans. by R. S. Creed. Oxford.
- [4] DENNY-BROWN, D. (1929). "On the Nature of Postural Reflexes," *Proc. Roy. Soc.*, **104B**, 252.
- [5] DENNY-BROWN, D. E. and SHERRINGTON, C. S. (1928). "Subliminal Fringe in Spinal Flexion," *Journ. Physiol.*, **68**, 175.
- [6] ECCLES, J. O., and SHERRINGTON, C. S. (1931). "Studies on the Flexor Reflex. II. The Reflex Response evoked by Two Centripetal Volleys," *Proc. Roy. Soc.*, **107B**, 535.
- [7] FULTON, J. F., LIDDELL, E. G. T., BLOCH, D. M. (1930). "The Influence of Unilateral Destruction of the Vestibular Nuclei upon Posture and the Knee-jerk," *Brain*, **53**, 327.
- [8] GRAY, L. P. (1926). "Some Experimental Evidence on the Connections of the Vestibular Mechanism in the Cat," *Journ. Compl. Neurol.*, **41**, 819.
- [9] LIDDELL, E. G. T., MATTHES, K., OLDBERG, E. and RUOH, T. O. (1932). "Reflex Release of Flexor Muscles by Spinal Section," *Brain*, **55**, 239.
- [10] MAGNUS, R. (1924). "Körperstellung," Berlin.
- [11] PAPEZ, J. W. (1926). "Reticulo-spinal Tracts in the Cat. Marchi Method," *Journ. Compl. Neurol.*, **41**, 865.
- [12] RASMUSSEN, T. H. (1930). "Direct Vestibulo-spinal Fibres in the Medial Longitudinal Fasciculus of the Cat," *Proc. Soc. Exper. Biol. Med.*, **27**, 771.
- [13] SHERRINGTON, C. S. (1910). "Flexion Reflex of the Limb, Crossed Extension Reflex, and Reflex Stepping and Standing," *Journ. Physiol.*, **40**, 28.
- [14] SHERRINGTON, C. S. and SOWTON, S. O. M. (1915). "Observations on Reflexes Responses to Single Break-shocks," *ibid.*, **49**, 331.
- [15] SPIEGEL, E. A. (1927). "Der Tonus der Skelettmuskulatur," Berlin.

REFLEX RELEASE OF FLEXOR MUSCLES BY SPINAL SECTION.

BY E. G. T. LIDDELL, K. MATTHES, E. OLDBERG AND T. C. RUCH.

(From the Laboratory of Physiology, Oxford.)

INTRODUCTION.

WHEN the spinal cord of a decerebrate preparation is transected at a low thoracic level, the flexor reflex undergoes immediate enhancement [9, 10]. The extensors, on the other hand, are depressed by spinal section [9]. For example, the knee-jerk becomes more susceptible to inhibition [1] and the stretch reflex disappears. This effect on the extensors has been traced to the vestibulo-spinal tract as the main agent, though there is a possibility that the reticulo-spinal tract plays an important subsidiary role [2, 11].

The spinal tracts whose section is responsible for release of the flexor centre remained for investigation and we now describe experiments performed with that object in view.

METHOD.

The animals used were cats, to the number of twenty. The experiments were acute, that is to say, the preparations were observed within a few minutes or hours of the spinal lesion. The animals were decerebrated under profound C.E. anaesthesia, the cord exposed by laminectomy at a low thoracic level and the usual immobilization of the hind limbs obtained by tendon or nerve resection for all muscles, except tibialis anticus in each leg. The ipsilateral popliteal nerve was prepared as an afferent for stimulation by Sherrington shielded electrodes. Some hours later, when the effects of the anaesthetic had worn off, the preparation was rigidly fixed by drills through the tibia and mounted under a shadow myograph of torsion-strip frictionless type. To elicit a single-shock flexor reflex the ipsilateral popliteal nerve was stimulated by a students' coil (coreless) with the secondary set at zero. A 2-v. accumulator fed the primary through a resistance box (P.O.), which was used to regulate the strength of stimulation. A Lucas pendulum broke the primary circuit. Two strengths of stimulation were sought, one

necessary to elicit a barely perceptible twitch (3 grm.), the other a twitch of 170 grm. active tension. The initial tension was 60 grm. In some earlier experiments, the strength of stimulus required was obtained by moving the secondary coil and not by altering the resistance in the primary circuit.

The dura mater was then opened and a selected part of the cord severed with a Saunders' discission needle at a low thoracic level. It was possible to place the lesion in the desired area. Its position was confirmed by subsequent examination after twenty-four hours' fixation in formalin. On occasion, the dura was opened before myographic examination, and immediately after laminectomy. At the same time a lesion of the cord was made. This alternative but less frequent procedure gave results in correspondence with the usual procedure. The lesion was usually made so as to be unilateral. By moving the preparation under the myograph, it was possible to examine each limb in succession. Before the infliction of any lesion, the difference between the two sides was very small. After a unilateral lesion, the change was almost entirely in the limb of the same side.

It has long been established that section of the cord in the lower thoracic region enhances the decerebrate rigidity of the forelimbs. Although we have made no specific observations on the tract concerned, the enhancement follows injury of ipsilateral tracts. Immediately or within five seconds of infliction of the lesion, the ipsilateral forelimb becomes rigidly extended forwards. Half a minute later, the contralateral forelimb follows suit.

In most preparations, making the lesion is followed by a short-lasting reaction and within two minutes spontaneous muscular movements cease and acceleration of the heart-rate comes to an end. In less favourable preparations, impairment of the circulation and respiration continues. It is well known that impairment of this kind alters the reflex background.

RESULTS.

Sherrington first described enhancement of the flexor reflex by (total) spinal section [9] and he and Sowton found that the enhancement is considerable, as a rule [10]. In non-rigid preparations, however, the change was often slight and sometimes lacking. We, too, found that enhancement of the reflex might reach, in most preparations, a very high value, e.g., ten times as measured by the ohmage in the primary circuit. These high values were obtained only in lesion of the cord of the same side. In none of our experiments did a lesion of the opposite

side of the cord ever effect more than a one-tenth increase in value, unless the lesion transgressed to the homolateral side. Sometimes a lesion of the opposite side produced a small *decrease* in excitability. The homolateral side has by far the more important influence in releasing the flexor centre. In only two preparations of our series did partial lesion fail to produce any change. But in these, complete section was also without effect. The release after the lesion is immediate and maintained for at least two hours, our longest observation. In some preparations the release became a little more marked during this time.

We found that when observations were taken in rapid succession, e.g., at two-second intervals, there was a very definite facilitation. A single-shock stimulus, for instance, when first applied might evoke a contraction of 4 mm., but if reapplied within two to three seconds the contraction rose to 5 mm., and did not, as a general rule, increase thereafter. It therefore became our custom not to record the first, but only subsequent responses.

This facilitation in the decerebrate preparation led us to investigate the state after tetanic stimulation. Facilitation was then considerable. Our method was as follows: A strength of stimulus was selected which gave, as a single shock, a contraction value of 170 grm. This was then applied as a tetanic stimulus (95 p.s.) for five seconds. At subsequent intervals the stimulus was then given as a single stimulus. In a typical response the tension was more than three times the original at an interval of one-minute after the tetanic stimulation, more than double at three minutes, and so continued for six minutes more. After twenty minutes from the onset, the threshold for 170-grm. twitch was still one-quarter of its original value. It was interesting to find that by cord section one and a quarter hours previously, the effect disappeared almost entirely, being only one-fifth more after thirty seconds, and normal after sixty seconds. The abolition of facilitation of this type therefore appears to depend on the severance of the paths from higher centres, and on the resulting deficiency of excitation reverberating from them.

In analysing the release resulting from partial spinal section, our experiments fall into two groups. In the first group, which is much the larger, one partial lesion, if restricted, never does more than half the threshold. In it are found the preparations in good physical condition circulation and respiration of which suffer little, if any, permanent impairment from the partial lesion. We describe the second group later in this paper. It comprises preparations in less good condition in which the threshold is lowered ten or twelve-fold by small spinal lesions.

Group I.—Our lesions were not always placed in definite areas, nor made in the same order. It was convenient for the purpose of assessing

Percentage, due to each area, of total change after complete spinal section.

Threshold for 170 grm. single shock reflex

The heavy underline denotes that those areas were transected by the same lesion. The index number at the end of the heavy line gives the order in which the lesions were made.

Ex. No.	Decerebrate before any ipsilateral lesion	After complete spinal section	Rise (ohms)	"Post."	"Post. Lat."	"Lat."	"Ant. Lat."	"Opp. Ant. Horn."	"Ant."
1	65	85	20	<u>100</u>	<u>100</u>	0'			
2	40	280	240	<u>58</u>	<u>58</u>	0'	0'	<u>37'</u>	<u>37</u>
					2				1
3	5	370	365	<u>16</u>	<u>16</u>		<u>2</u>	<u>2</u>	<u>2</u>
					2				1
					82'	82'			
						3			
4	5	159	154		<u>76</u>	<u>76</u>			
						1			
				0	0	0	0	0	<u>26</u>
								2	3
5"	140	400	260		<u>40</u>	<u>40</u>	<u>60</u>	<u>60</u>	<u>60'</u>
						1			2
6	0	370	370	<u>100</u>	<u>100</u>	0	0	0	0*
					4		3	1	2
7	30	320	790	<u>0</u>		<u>0</u>			
				2		1			
8	5	140	135	<u>0</u>	0	0	0	<u>75</u>	<u>75'</u>
				3			2		4
									25'
									5
9	10	360	350	0'		<u>0</u>		<u>45</u>	<u>45</u>
						1			3
					55		55		
							2		
10*	12.6 cm.	24.6 cm.	12 cm.	<u>75</u>	<u>75</u>	(approx.)			

Average rise in threshold for injury in each area, but the figure must be offset against the per cent. frequency of zero change	38	54	20	17	31	39
	44	11	66	71	43	29

(') Values obtained by semi- or total section at conclusion of experiment.

(") Semi-section of opposite side during morning.

(*) Superficial lesion.

(*) An early experiment when strength of shock was graduated by moving the secondary coil.

results to map the cord into areas as shown in fig. 1. Since a lesion was often made to pass through more than one area, it is possible that an inactive area bordering on an active area might acquire an undeserved reputation. This has been counteracted by showing the number of times on which lesions of the areas gave no change. Thus it appears that any lesion on the ipsilateral side can on occasion lower the reflex threshold. There are, however, two regions of special susceptibility which also are constant in showing susceptibility and seldom show no change at all. These regions are the postero-lateral and the anterior.

In the above experiments, there was no tetanizing stimulation of the preparation for the establishment of facilitation (p. 241). Facilitation experiments have been discarded for purposes of this assessment. The changes recorded were due only to the spinal lesion.

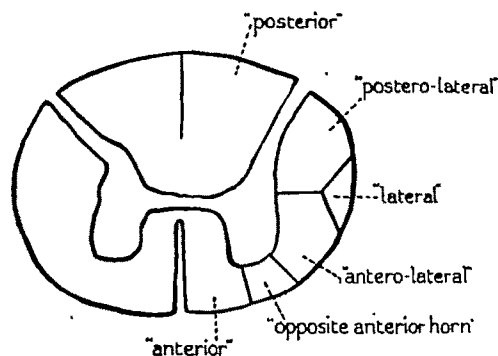


FIG. 1.—To show diagrammatically the regions described in the text.

Postero-lateral region.—In considering the anatomical tract in this region whose section might bring about release, it is possible to eliminate the pyramidal tract, which although present in the cat in the lower dorsal region, cannot be involved since it has been sectioned already by the decerebration. Also, in most of our preparations, it was possible definitely to exclude the rubrospinal tract since the level of decerebration was often at or caudal to the intercollicular level, so that the greater part of the red nucleus was already ablated, and any part which might remain would suffer considerable impairment from oedema and exposure. The tract with which we are concerned is not near the surface of the cord since superficial lesions do not establish any striking release. But an important descending tract which is located deep in the postero-lateral region is the lateral reticulo-spinal (fig. 2). By the degeneration experiments of Papez [7] and Gray [5], it is seen to be a considerable

link between the reticular formation of the medullary region and the lower spinal centres [8]. Since we find, by physiological experiment, that the area through which the tract runs is one whose section gives release to flexor centres from higher control, we conclude that the lateral reticulo-spinal tract is probably itself the path by which impulses descend in the decerebrate preparation to check flexor activity. The uncinate fasciculus of Russell, which occupies the same region as the lateral reticulo-spinal tract, does not descend lower than the level of the second cervical nerve and can therefore be disregarded for present purposes.

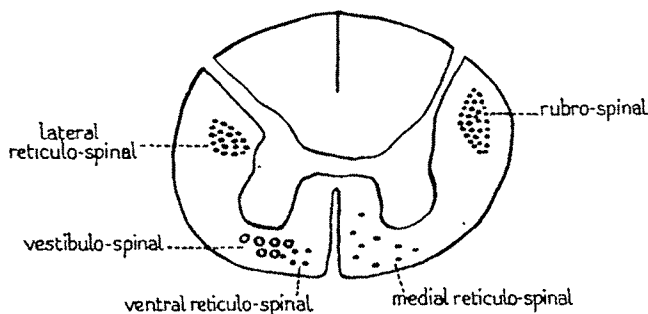


FIG. 2.

Anterior region.—In the production of spinal shock in extensor muscles and their increased susceptibility to inhibition after spinal section, Fulton, Liddell and Rioch [4] established the importance of the vestibulo-spinal tract, although that was probably not the only tract, because section of the vestibular tract itself was less effective than section of the anterior quadrant of the cord [cf. 11]. In view of their results, it might be expected *a priori* that the same tracts would be concerned in the release of the flexor centres from higher control, and we have found, as pointed out above, that the anterior region of the cord is susceptible as well. In an accompanying paper, where experiments are described in which the vestibular nerve was sectioned intracranially, evidence is presented that those tracts have this function also for flexors [6]. In addition, the ventral and medial reticulo-spinal tracts (see fig. 2) are in all probability concerned, though their relative importance has not been estimated. The vestibulo-spinal tract extends rather more laterally than the ventral reticulo-spinal and its coming into our anterior area would account for the constant moderate release achieved by section in that area.

As mentioned above, we have not found any considerable or constant release from sections of the cord on the opposite side. Although there are crossed reticulo-spinal tracts and also slender crossed vestibulo-spinal tracts, their decussations are well above the level of the spinal cord and therefore above the level of our lesions.

Group II.—In assessing the second group of results, in which there were falls of threshold as much as ten-fold, impairment of the preparations, circulation and respiration seemed to be an important accompaniment. The average of this series for the posterior funiculi is a four-fold increase, for the other funiculi six to seven-fold without clear differentiation. Certain preparations, therefore, are so unstable that any considerable division of any path in the postero-lateral and anterior regions is likely to give an apparent, even if not a direct, release. But such preparations are only obtained from animals in imperfect health, with an impaired vascular system, and taken from an unselected laboratory stock. The release in such cases is the maximum possible for that preparation. These unstable preparations giving maximum release are therefore less useful than the more resistant preparations for purposes of relative assessment.

SUMMARY.

The enhancement of the flexor reflex in decerebrate preparations resulting from total spinal section is due, in fact, to transection of two susceptible ipsilateral regions, the postero-lateral and the anterior. The tract in the postero-lateral region is probably the lateral reticulo-spinal tract, and in the anterior region the vestibulo-spinal and ventral and medial reticulo-spinal tracts are probably chiefly concerned.

REFERENCES.

- [1] BALLIEF, L., FULTON, J. F., and LIDDELL, E. G. T. (1926). "Observations on Spinal and Decerebrate Knee-jerks with Special Reference to their Inhibition by Single Break-shocks," *Proc. Roy. Soc.*, **98B**, 589.
- [2] CAMIS, M. (1930). "Physiology of the Vestibular Apparatus." Trans. by R. S. Creed, Oxford.
- [3] DANNY-BROWN, D. (1928). "On the Nature of Postural Reflexes," *Proc. Roy. Soc.* **104B**, 253.
- [4] FULTON, J. F., LIDDELL, E. G. T., and RIOCH, D. M. (1930). "The Influence of Experimental Lesions of the Spinal Cord upon the Knee-jerk. I. Acute Series," *Brain*, **53**, 811.
- [5] GRAY, L. P. (1926). "Some Experimental Evidence on the Connections of the Vestibular Mechanism in the Cat," *Journ. Comp. Neurol.*, **41**, 319.
- [6] LIDDELL, E. G. T., MATTHEWS, K., OLDBERG, E., and RUCH, T. O. (1932). "The Influence of Section of the Vestibular Nerve on the Single-shock Reflex Flexor Response." *Brain*, **55**, 232.

- [7] PAPPEZ, J. W. (1926). "Reticulo-spinal Tracts in the Cat. Marchi method," *Journ. Compt. Neurol.*, **41**, 365.
 - [8] RASMUSSEN, T. H. (1930). "Direct Vestibulo-spinal Fibres in the Medial Longitudinal Fasciculus of the Cat," *Proc. Soc. Exper. Biol. Med.*, **27**, 771.
 - [9] SHERRINGTON, C. S. (1910). "Flexion Reflex of the Limb, Crossed Extension Reflex, and Reflex Stepping and Standing," *Journ. Physiol.*, **40**, 68.
 - [10] SHERRINGTON, C. S. and SOWTON, S. C. M. (1915). "Observations on Reflex Responses to Single Break-Shocks," *Ibid.*, **49**, 831.
 - [11] SPIEGEL, E. A. (1927). "Der Tonus der Skelettmuskulatur," Berlin.
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SPASTIC PSEUDOSCLEROSIS (CORTICO-PALLIDO-SPINAL DEGENERATION).¹

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I.—INTRODUCTION.

THE clinician and the pathologist are occasionally confronted with morbid processes which do not conform to any of the recognized clinical syndromes. I have recently seen two such cases. The disease occurred in two adults; it ran a rapid course; and it was characterized clinically by mental symptoms, pyramidal and extrapyramidal signs, and muscular atrophies. Histopathologically, there were changes in the nervous system corresponding to these clinical findings. These two cases at one time were considered with four others as unusual instances of amyotrophic lateral sclerosis with mental symptoms. The extrapyramidal symptoms and the histopathological changes found in the pallidum make it doubtful if they belong to this group.

II.—REPORT OF CASES.

Case 1.—J. R., male, aged 32, was admitted to the hospital on May 30, 1930. In December, 1927, he noticed the onset of weakness and unsteadiness of the left lower extremity which remained unchanged until April, 1929, when, following a sore throat, he developed difficulty in speech and weakness of the upper extremities. Examination in November, 1929, showed gluteal atrophy, exaggeration of all deep reflexes, more on the left, a left Babinski sign, left facial weakness, deviation of the tongue to the left, marked dysarthria, dysmetria of the left upper extremity, spastic ataxia of the left leg, and a slowness and slurring of speech. Multiple sclerosis or a degenerative disease of the nervous system were considered as diagnostic possibilities. There was no history of influenza or encephalitis. The family and past history were unimportant.

Neurological examination in May, 1930, revealed a bedridden young adult with rigidity, drooling, spasmodic laughing and crying, and unsteadiness of the upper limbs. The speech was dysarthric, explosive, scanning, and at times

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monotonous. The interosseous muscles were atrophied and there were generalized fibrillary twitchings, massive in character, of the arms, forearms, hands, legs, shoulders, and girdle muscles. There was increased tonus in all four limbs, and cog-wheel rigidity in the upper limbs. The left foot had a striatal attitude. Power was diminished in all extremities, more on the right side. There was generalized bilateral increase of the reflexes with positive Babinski sign and absent abdominal reflexes. The fundi were normal. The face was oily. The right corner of the mouth drooped. Emotional movements were good. The tongue deviated to the left. The patient was deteriorated, apathetic, inco-operative, and disoriented. His memory was poor for recent and remote events. He usually responded to simple commands, but more complicated ones elicited no response whatsoever.

His other organs were normal. X-rays of the skull showed a faint streak of calcification above and to the right of the pineal gland. The possibility of a neoplasm was considered. All other laboratory data were negative.

The patient gradually developed difficulty in swallowing and breathing. On November 7, 1930, he developed fever and cyanosis, and died of aspiration pneumonia the following day.

Pathological findings: Permission for the removal of the brain and spinal cord only was obtained.

Brain.—The convolutions from the frontal to the post-central regions were atrophic and the fissures were widely separated. The blood-vessels were markedly congested. The cortical gray matter appeared thin. The white matter of the right corona radiata, in sections through the caudate and putamen, was shrunken.

Spinal cord.—The cord appeared anæmic. On transverse section there was translucency of the crossed pyramidal tracts. The gray matter was slightly hæmorrhagic.

The brain and spinal cord were preserved in 10 per cent. formaldehyde. Frozen and celloidin sections from the entire nervous system were stained by the myelin sheath stain (Weil modification), Mallory's phosphotungstic and hæmatoxylin, hæmatoxylin-eosin, cresyl violet, Sudan IV, Cajal's gold sublimate (Globus modification), Bielschowsky's, Del Rio-Hortega's (Penfield's modification) and Anderson's Victoria blue methods.

Microscopical Examination.

Cerebral hemispheres, frontal lobes.—The pia-arachnoid was thickened in places and there was proliferation of the arachnoidal cells. The meningeal vessels showed moderate atherosclerotic changes. The arrangement of the cortical architectural layers was fairly well preserved. The ganglion cells of the third, fifth and sixth layers were diminished in number. Some cells were shrunken, had deeply stained nuclei, reticular protoplasm and corkscrew processes; others were swollen, the nuclei were at the periphery of the nerve-cells, and the tigroid substance had disappeared completely. The cells of the fifth layer were more involved than those in the other layers. The nerve-cells

in this area were completely disintegrated and showed marked chromatolytic changes. With the Sudan IV stain lipid granules were found in the ganglion cells. Definite foci of destruction were present. There was an increase in the smaller vessels of the cortex, a few showed intimal proliferation, and some were completely occluded. There was an enormous proliferation of microglia cells in the third, fifth and sixth cortical layers; some were hypertrophied (fig. 1). The protoplasmatic astrocytes were also increased in number. The white matter, particularly on the right side, stained poorly, but did not show any evidence of breaking down of myelin. The Cajal gold sublimate stain of the white matter disclosed numerous enlarged astrocytes.

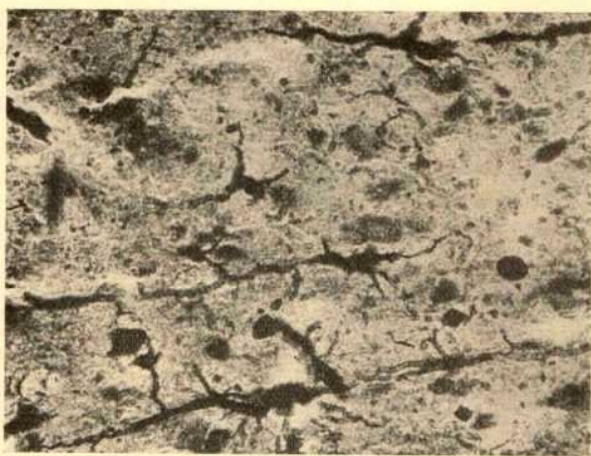


FIG. 1.—Increased and hypertrophied microglia cells in the cortex. Silver carbonate stain (Penfield's modification). $\times 400$.

Precentral gyrus.—The same changes were observed as in the frontal gyri, except that the normal architectural arrangement of the cortical laminae was lost. The giant pyramidal cells of Betz were fewer in number, were disintegrated, and had ill-defined nuclear bodies and very little Nissl substance. There was also neuronophagia. The capillaries, microglia and protoplasmatic astrocytes were increased in number. There were no giant astrocytes. The white matter was filled with proliferated and occluded small vessels, some of which showed evidence of beginning calcification.

Hippocampus.—There was falling out of ganglion cells with the changes seen in the acute and chronic stages of degenerative diseases. Occasional neuronophagia was also observed here. The microglia and protoplasmatic astrocytes were increased in number.

Sections from the parietal, temporal and occipital regions, except for occasional poorly-stained ganglion cells, showed nothing of note.

Basal ganglia.—The caudate nuclei were normal. Putamen: The small and

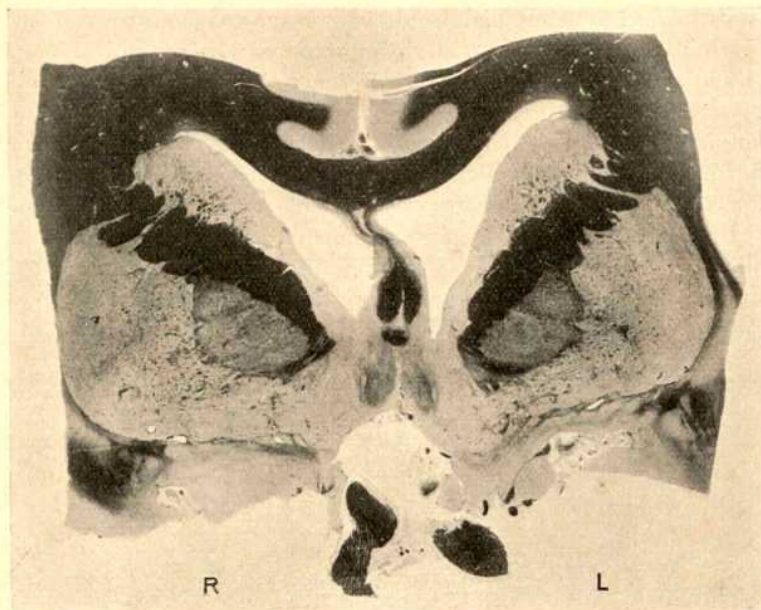


FIG. 2.—Section through the neostriatum and rostral end of the globus pallidus showing poorly stained white pallidal fibres, more so on the right. Myelin sheath stain (Weil modification).



FIG. 3.—Disintegration of the white fibres from the globus pallidus. Myelin sheath stain (Weil modification). $\times 480$.

large ganglion cells were fewer in number, some showed loss of Nissl substance and eccentrically placed nuclei, and others were completely disintegrated. Neuronophagia was rarely observed. The nerve cells of the amygdaloid nuclei appeared normal. *Globus pallidus*: The white fibres of the globus pallidus took the myelin sheath stain poorly (fig. 2). Under higher magnification some of the pallidal fibres, especially those on the right, were demyelinated. Some of the myelin sheaths were completely broken down and others were swollen (fig. 3). A number of the vessels were markedly sclerosed and calcified (fig. 4a). About the calcified vessels the pallidal cells were decreased in number, shrunk,



FIG. 4a.

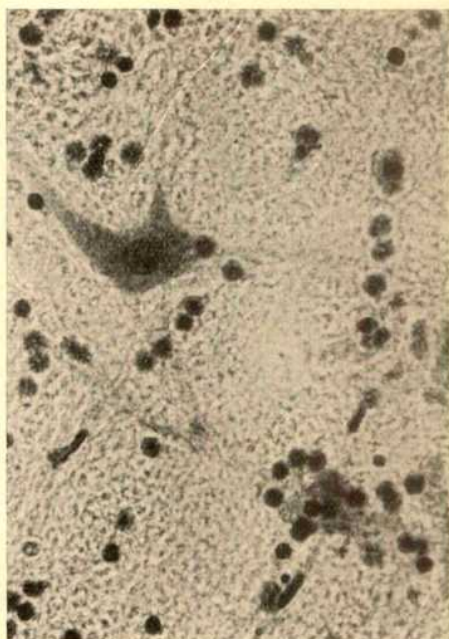


FIG. 4b.

FIG. 4a.—Section from the globus pallidus showing calcification of the blood-vessels and decrease in the number of ganglion cells. Cresyl violet stain. $\times 120$.

FIG. 4b.—Two ganglion cells from the globus pallidus; one showing satellitosis, and the other poor chromatin substance. Cresyl violet stain. $\times 700$.

had a homogeneous appearance, showed poor chromatin substance and some were completely destroyed. Some of the ganglion cells showed vacuolation. Occasional neuronophagia was also observed (fig. 4b). In places there was a slight increase in the number of protoplasmatic astrocytes and microglia. A few amyloid bodies were seen. Most of these changes were found in the rostral and middle portions of the globus pallidus.

Corpus Luysii.—The same changes were found here as in the globus

pallidus, but not quite so marked. There were no calcified vessels and the nerve-cells were somewhat better preserved. The superior part of the right internal capsule contained a few vessels with round-cell infiltration in the perivascular spaces.

The paraventricular nuclei.—The nerve-cells showed marked destruction, otherwise the changes were about the same as those observed in the cortex and globus pallidus.

The thalamus, substantia innominata of Reichert, red nucleus and substantia nigra were normal.

Sections in the region of the posterior commissure and pons.—The pyramids were poorly stained. With higher power some of the myelin sheaths of the

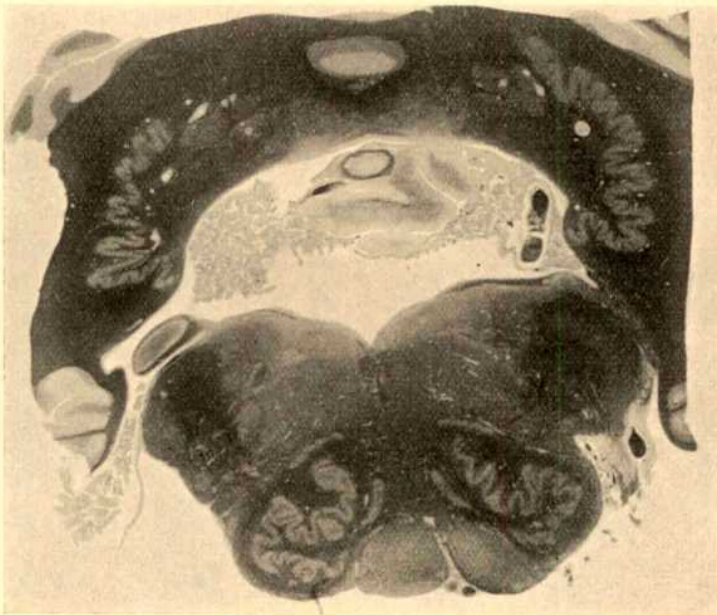


FIG. 5.—Lacunar state in the region of the dentate, emboliform and globose nuclei. Demyelination of the pyramids in the medulla oblongata. Myelin sheath stain (Weil modification).

pyramidal fibres appeared disintegrated. Sections in the region of the colliculi, cerebellum and pons showed marked thickening and fibrosis of the pia-arachnoid. Psammoma bodies were found within this fibrosed tissue. The white matter of the cerebellum did not take the myelin sheath stain well and with higher magnification occasional fibre disintegration could be observed. The architectural layers of the cerebellum were well preserved, except for poor staining of the Nissl substance in the Purkinje cells. The dentate, emboliform and globose nuclei presented a lacunar appearance (fig. 5). A few of the nerve-cells of the dentate nucleus showed changes similar to those found in the

cortex. The pyramids of the medulla oblongata were demyelinated (fig. 5). Some of the myelin sheaths were broken down and others showed signs of swelling. The cells of the nucleus ambiguus were fewer in number, showed poor Nissl substance, eccentric nuclei and occasional neuronophagia. The nuclei of the other cranial nerves presented very slight changes. The nerve-cells of the superior and inferior olives were intact.

Spinal cord.—Sections at various levels showed demyelination of both crossed and the right anterior pyramidal tracts (fig. 6). With higher magnification the changes previously described in the pyramids were found, and in addition a honeycomb appearance and a more advanced disintegration of the myelin. In the Bielschowsky preparation the axis-cylinders were completely broken

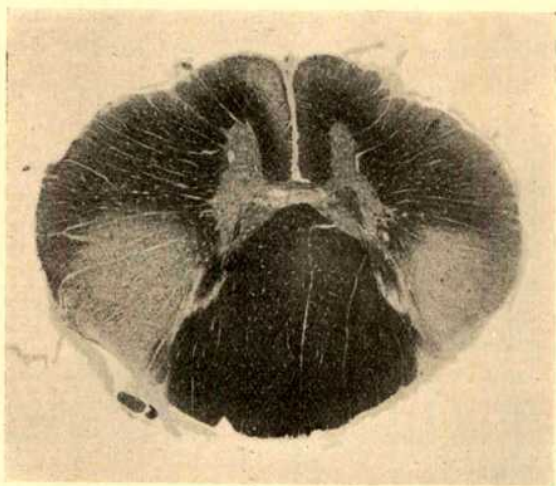


FIG. 6.—Transverse section of the spinal cord in the mid-thoracic region, showing demyelination of the lateral pyramidal tract and the right anterior pyramidal tract. Myelin sheath stain (Well modification).

down and had a corkscrew appearance. The demyelinated areas were replaced by densely packed glia fibres. The anterior horn cells were decreased in number; some were shrunken, amorphous, deeply stained and devoid of Nissl substance. Homogenization and collection of tigroid substance at the periphery, with eccentrically placed nuclei, were also observed. There was a slight increase in the glia cells within the gray matter. These changes were observed throughout the spinal cord, except in the sacral region.

Comments.—The diagnosis rested at first between multiple sclerosis, the lenticular syndrome (Wilson's disease or pseudo-sclerosis) and amyotrophic lateral sclerosis with mental symptoms. The histopathological findings were: atrophy of the cerebral convolutions from the frontal to the parietal regions; scantiness and destruction of the ganglion cells in

the third, fifth and sixth layers; areas of devastations; proliferation of the vessels; increase in the microglia and protoplasmatic astrocytes of the cortical gray matter and in the astrocytes of the white matter; marked destruction of the giant pyramidal cells of Betz; demyelination of the pallidal fibres; calcification of the pallidal vessels; destruction of the nerve cells of the pallidum, corpus Luysii and paraventricular nuclei; degeneration of the pyramidal tracts and degenerative changes in the anterior horn cells. There was no evidence of encephalitis. The few inflammatory cells found in the perivascular spaces of the internal capsule could have no bearing on this disease process. There were no giant glia cells as observed in Alzheimer's disease or pseudo-sclerosis. The histopathological changes resembled the findings in the latter two diseases, except for the absence of plaques and giant glia cells. The pathological findings in the spinal cord were those of amyotrophic lateral sclerosis.

Case 2: E. G., female, aged 50, was admitted to the hospital on July 19, 1930, in a semi-stuporous condition, with a temperature of 104° F., and died the next day. In January, 1929, she complained of headache and pain in both shoulders radiating to the lumbar region. At the beginning the pain was mild, later it became severe. In May, 1929, she had difficulty in walking and spasticity of the lower extremities. She also complained of polydipsia and polyuria. Two months before admission to this hospital she became drowsy and mentally confused. At two other institutions the diagnosis first of multiple sclerosis and later of diffuse degenerative disease with mental symptoms was made.

Neurological examination was unsatisfactory because of the mental stupor. She presented a coarse and greasy skin, a tendency to bilateral ptosis, right facial paralysis, spastic paresis of all four extremities, generalized increase of the deep reflexes, bilateral Babinski sign and absent abdominal reflexes, dysmetria, Parkinsonian facies with rigidity of the upper extremities, a tendency to the accoucheur position of the hands and catatonia. Mentally, the patient was confused, co-operated very poorly, showed psychomotor retardation and was emotionally unstable.

Except for a slight secondary anæmia and a trace of albumin in the urine, all other laboratory findings were negative.

Pathological findings: All the organs, except the nervous system, showed a moderate generalized arteriosclerosis. The liver was normal.

Brain.—There was slight atrophy of the convolutions, more on the right, extending from the frontal to the post-central gyri. The fissures in these areas were widely separated and the vessels were congested.

Spinal cord.—The dura was slightly thickened and its inner surface was studded with numerous calcareous bodies. There was a translucency of the

right lateral pyramidal tract in the cervical, mid and lower thoracic regions. Frozen and celloidin sections of the entire nervous system were stained with the same methods as in Case 1.

Microscopical Examination.

Cerebral hemispheres.—Sections of the frontal convolutions showed normal meninges with moderately atherosclerotic vessels. There were no disturbances in the arrangement of the architectural layers of the cortex. The ganglion cells of the fifth and sixth layers were diminished in number. They stained very poorly, were swollen and totally devoid of Nissl substance (fig. 7)



FIG. 7.—Swelling of the ganglion cells from the frontal convolution, eccentric nuclei and poor Nissl substance. Cresyl violet stain. $\times 700$.

The nuclei of most of the ganglion cells of these layers were likewise swollen and eccentric and contained little chromatin. Throughout the fifth and sixth laminae there was hardly a normal cell. A few of the ganglion cells of the third layer showed similar changes. With the Sudan IV stain lipoid granules were found in the nerve-cells. The glia cells were slightly increased in the third, fifth and sixth layers, and consisted primarily of protoplasmatic astrocytes. Contrary to the findings in Case 1 there was no increase in microglia here. The white matter appeared normal. The larger vessels showed moderate atherosclerotic changes. The smaller capillaries were increased in number as in Case 1 (fig. 8).

Precentral convolutions.—There was a falling out of the ganglion cells in practically all the layers, most noticeable in the fifth and sixth laminae. The architectural layers were not as well preserved as in the frontal gyri. The giant pyramidal cells of Betz were fewer in number and showed chromatolytic

changes. The more minute histological changes in the ganglion cells were the same as in the frontal region.

Parietal and temporal areas.—Except for marked disarrangement in the cortical layers these showed the same changes as in the previous sections. The gray and white matter of the temporal lobes were studded with numerous lacunæ. The white fibres did not take the myelin sheath stain as well as in the previous sections, although there was no breaking down of myelin. The architectural layers in the middle temporal lobes could barely be made out, and the falling out of ganglion cells and chromatolytic changes were predominant in the third layer, instead of the fifth and sixth as in the other regions. The hippocampus was loaded with numerous corpora amylacea, poorly stained

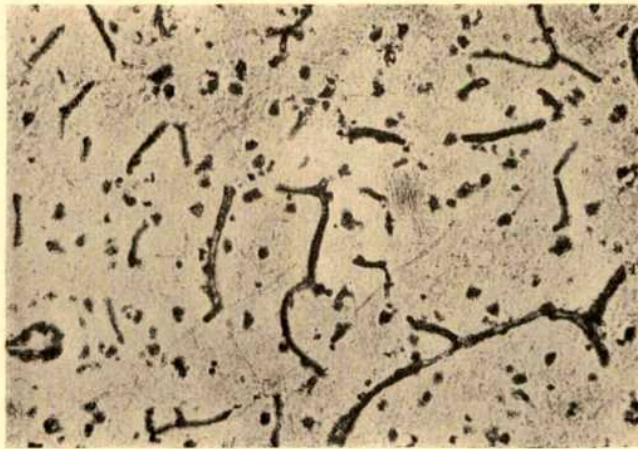


FIG. 8.—New vessel formation in the cortex. Silver carbonate stain. $\times 200$.

ganglion cells, and a few calcified vessels. In the occipital lobes very slight changes were observed.

Basal ganglia.—With the myelin sheath stain the right globus pallidus had a lacunar appearance, and the white fibres stained poorly (fig. 9). Some of these fibres were completely demyelinated. The ganglion cells in the neostriatum, thalamic and paraventricular nuclei, except for an occasional poorly stained cell, were well preserved. In the globus pallidus, however, both the ganglion and the glia cells were diminished in number. The pallidal cells showed acute and chronic changes as swelling, lack of chromatin, homogeneous appearance, and occasional shrinkage and pyknosis. The nuclei were swollen, poor in chromatin material and eccentrically placed. Throughout the pallidum, especially in the inner segment of the middle and caudal parts, numerous calcified blood-vessels were found. Most of the changes of the ganglion cells were found in the vicinity of the calcified vessels. There were no amyloid bodies. New vessel formation, as in the cortex, was also observed here. With the

Sudan IV stain fat was observed in the vessels. The cytoplasm of the nerve-cells was replaced by lipid granules. The protoplasmatic astrocytes were slightly increased in number.

The corpus Luysii, substantia nigra, and red nucleus.—Except for an occasional disintegrated or poorly stained ganglion cell, these structures showed no abnormalities. A few of the nerve-cells in the oculomotor nerve nuclei showed evidence of pigment atrophy.

The cerebellum and pons showed no changes. Except for occasional loss in Nissl substance and pigmentation, the ganglion cells of the dentate nuclei were normal.

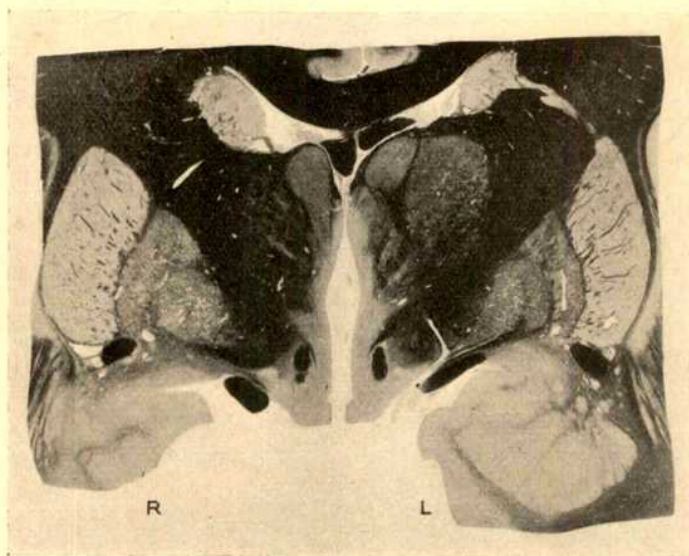


FIG. 9.—Section through the middle third of the globus pallidus showing paleness and a lacunar state of the right inner segments of the pallidum. The white fibres of the globus pallidus on that side did not take the stain well. Myelin sheath stain (Weil modification).

Medulla oblongata.—The pyramids were pale. The nerve-cells of the tenth and twelfth nerve nuclei showed chromatolysis, shrinkage, vacuolation and pigmentary atrophy. The same changes were found in the inferior and accessory olivary nuclei. The nerve-cells of the locus cœruleus contained very little pigment.

Spinal cord.—In sections throughout the cord there was marked demyelination of both crossed pyramidal tracts and to a lesser extent also of the left uncrossed pyramidal tract (fig. 10). A number of the myelin sheaths were completely destroyed and others swollen. Many axis-cylinders were broken down, some had a corkscrew appearance, but a few were fairly well preserved. The glia fibres of the lateral pyramidal tracts were increased in number. The

anterior horn-cells were diminished in number, some were markedly swollen, had a homogeneous appearance, were devoid of Nissl substance, and had swollen and eccentrically placed nuclei. Those of the mesio-ventral group showed poor Nissl substance and atrophy. These changes in the ganglion cells were observed throughout the spinal cord, except in the sacral region, and were most marked in the thoracic region. The vessels were normal, the meninges were not thickened, and there was no evidence of any perivascular infiltration.

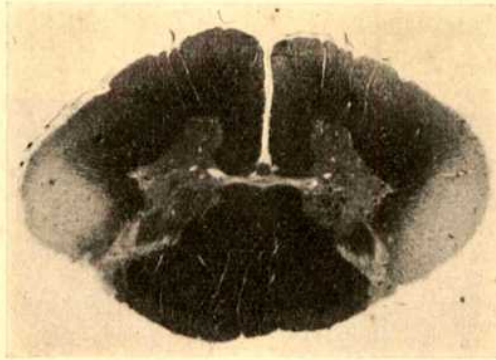


FIG. 10.—Transverse section of the spinal cord showing demyelination of the lateral pyramidal tracts. Myelin sheath stain (Weil modification).

Comments.—This patient, as in Case 1, showed mental symptoms, Parkinsonian facies, rigidity of both upper extremities, absent abdominal reflexes, and pyramidal tract signs. Atrophy of the muscles was not observed. The diagnosis of multiple sclerosis or degenerative disease of the nervous system was considered. The histopathological changes, except for minor differences, were almost the same as in Case 1. The third layer of the cortex was less involved than the fifth and sixth layers, and there was no increase in the microglia cells of the cortex. The temporal lobes showed more marked changes than in Case 1. There was absence of corpora amylacea in the pallidum, and no changes in the corpus Luysii, paraventricular and dentate nuclei. There was no evidence of inflammatory cells in any of the sections. Giant glia cells, as found in Alzheimer's disease or pseudo-sclerosis, were not seen. The pathological changes in the spinal cord were similar to those found in amyotrophic lateral sclerosis.

III.—DISCUSSION.

Review of literature.—Creutzfeld [1] in 1920, and Jakob [2] in 1920 and 1921, described a series of cases which were designated by

Jakob as "spastic pseudo-sclerosis." The disease occurred in middle age or later, and consisted of slowly-developing disturbances of the motor and sensory functions, and changes in personality, as anxiety, irritability, and depression. At first the disease gave the impression of being functional. The patients soon complained of weakness, pain and stiffness of the legs. On attempting to walk, they frequently fell; gait was spastic. The abdominal reflexes were diminished or absent. In most cases remissions occurred. Gradually the motor disturbances became more distinct; there was a mixture of spastic and thalamo-striatal features. At first, gait was incoördinate, and toward the end the patients could neither walk nor stand. Hypotonia of the extremities was observed in some of the cases. Distinct striatal symptoms, such as slow spontaneous movements, rigidity, tremor and athetosis, were outstanding features. The speech was slow, monotonous, and usually dysarthric. The tendon reflexes were usually increased, but in some patients they were normal or even absent; the Babinski reflex in certain stages of the disease was positive. The fundi remained unchanged. The blood and cerebrospinal fluid were normal. Toward the end, the mental symptoms became more marked, and consisted of apathy, negativism, delirium, confusion, visual and auditory hallucinations, and confabulations, which reminded one of Korsakoff's syndrome. Cerebral irritative symptoms, involvement of the bulbar nuclei, decubitus ulcers, marked stupor and fever, brought the disease to an end. The evolution of the disease was comparatively rapid, lasting from several weeks to a year.

Pathologically, this syndrome, as described by Jakob, was characterized by widely disseminated lesions involving mainly the frontal, temporal and precentral convolutions, the corpus striatum, the ventromedial nuclei of the thalamus, the bulbar nuclei and the anterior horn cells. The changes were non-characteristic ganglion cell degeneration, fatty degeneration, swelling, neuronophagia, glia rosettes, outfall of ganglion cells and small areas of devastation (Verödungsherde). There was generalized proliferation of protoplasmatic glia, especially in the last three cortical layers. As a result of the lesions of the giant pyramidal cells of Betz in the precentral gyrus, there was a slight descending degeneration of the pyramidal tracts of the spinal cord.

The clinical diagnosis in all these cases varied between multiple sclerosis, general paralysis, Alzheimer's disease, dementia præcox, and pseudo-sclerosis. At first the disease was considered functional. From the pathophysiological and clinical points of view, according to Jakob,

the disease belongs to the spastic system type, especially amyotrophic lateral sclerosis, and to the strio-pallidal group. Jakob, because of the pyramidal tract signs, designated the disease as spastic pseudo-sclerosis, to differentiate it from the pseudo-sclerosis of Westphal-Strümpell. The giant glia cells (Alzheimer's cells) found in pseudo-sclerosis were not seen in this new syndrome.

Alzheimer [3] (1916) described a case which belongs to the same group. The brain in this patient did not show the marked changes found in the cases of Creutzfeld and of Jakob. There were compound granular corpuscles throughout, and giant glia cells in the globus pallidus which did not resemble those seen in pseudo-sclerosis. Von Economo and Schilder [4] (1920) reported a case which evidently belongs to this group. The striatal symptoms were more prominent, and pyramidal tract signs were absent. In addition to disseminated lesions in the brain (the spinal cord was not examined), the authors described an interstitial hepatitis, and considered a diagnosis of pseudo-sclerosis or Wilson's disease. Stauffenberg [5] in 1918 published a case of olivo-ponto-cerebellar atrophy which may also be placed in the Creutzfeld-Jakob group. Woerkom [6] reported two patients similar to those described by Von Economo and Schilder; in each the liver was involved. Fleishaker [7] (1924) recorded one case with similar findings, but felt that it belonged to the paralysis agitans group. Kirschbaum [8] (1924) also published two cases, and named them spastic pseudo-sclerosis (Jakob).

Each of my two cases had a clinical course somewhat similar to those described by Creutzfeld, Jakob and others. The mode of onset, the age, the absence of obvious cause, the mental changes, the motor disturbances, the absence of the abdominal reflexes, the striatal symptoms and the short duration of the disease were similar. The minor clinical differences consisted in the absence of sensory disturbances in my first case, the absence of remissions, the presence of the Babinski sign throughout instead of in certain stages only of the disease, and the appearance of the mental symptoms late in the course of the disease. Histopathologically the differences were more striking. In my two cases pronounced lesions of the thalamic nuclei, marked neuronophagia and glia rosettes were not found. Giant glia cells, as observed by others, were absent in my cases. None of Jakob's cases showed the new vessel formation in the cortex and pallidum. Microglial proliferation as found in my first case was only observed in Case 1 of Creutzfeld. In contrast to Case 1 and the Creutzfeld Jakob group, Case 2 did not show marked

glial proliferation. None of the authors described calcification of the pallidal vessels and the status demyelinatus of the globus pallidus.

Calcification.—A number of pathologists agree that focal and perivascular calcification occurs wherever there is degeneration. This process has been observed in various conditions, such as epidemic encephalitis, idiocy, carbon monoxide poisoning, malaria and diseases in presenium. Other observers maintain that the deposition of the calcium is a secondary occurrence and that it has no relationship to the pathological process. They point out the fact that the tissue surrounding the calcified vessels remains intact. Hurst [9] has shown that the richness of the globus pallidus in iron is very likely related to a gross and often striking infiltration of its vessel walls by calcium salts, a condition found by him in fifty out of a hundred brains from cases of chronic nervous disorders. Hallevorden and Spatz [10] think that the deposition of the pigment in the pallidum and in the substantia nigra in certain cases is a pathological exaggeration of a condition normal to those structures and indicating a close physiological relationship between them. They regard the pigment as a product of metabolism and attribute its formation to neuroglial nuclei. Urechia and Elekes [11], who found calcification in the vessels of the lenticular nucleus in cerebral syphilis, believe the deposit to consist of fatty acids, iron and calcium. Lhermitte, Kraus and McAlpine [12] found deposits giving an iron reaction in the vessels of the anterior half of the globus pallidus in encephalitis lethargica. Spielmeyer [13] considered the deposition of calcium in the adventitia of cerebral vessels a common change in chronic disease, in old atrophic areas, and also in acute processes such as carbon monoxide poisoning and encephalitis lethargica. Cerebral calcification has been also described by Bassoe and Hassin [14] and by Geyelin and Penfield [15]. The latter is of the opinion that in his cases there was probably a slowly progressive closure of the end arteries in the cerebrum, producing an area of local necrosis, chiefly at the level at which the short pial vessel supply ends and the deeper blood supply begins. This area of degeneration then becomes secondarily calcified, and calcium is laid down in the walls of the vessels. Hadfield [16], in an extensive investigation, concludes that the walls of the blood-vessels of the healthy globus pallidus are often infiltrated with iron salts which are derived from the nucleus itself. He considers the likelihood that the process is one of involutionary atrophy and that it predisposes to the acute bilateral destruction of these nuclei so frequently observed in coal-gas poisoning.

The reports of numerous investigators and the findings in cases of other neurological disorders from this laboratory, suggest strongly that the calcification of the vessels in the globus pallidus of my two cases was secondary to the pathological process. The degeneration in the pallidum, which was due to the same agent as that of the rest of the central nervous system, caused a secondary calcification. The calcium was deposited in the walls of the vessels. The secondary calcification of the vessels leads to further destruction of the pallidum, as evidenced by the marked change found in the pallidal cells, and the status demyelinatus.

Status demyelinatus.—Cécile and Oskar Vogt [17] described under the term "status demyelinatus" a process in which there is a poverty of the white fibres of the striatum, especially those of the pallidum. It starts in childhood and leads to a progressive rigidity. The same process was described in juvenile cases by Fischer [18], Rothmann [19], Hallervorden and Spatz [20], Kalinowsky [21], Fungfeld [22], Onari [23], Lhermitte and Von Bogaert [24], Winkelman [25], and others. Hallervorden and Spatz [20] described the status demyelinatus in five children of the same family, the disease appearing between the ages of 7 and 9. Kalinowsky reported the condition in three sisters in whom the disease began at the ages of 9 to 10. In Fungfeld's case the disease was noticed at the age of 25, and Onari's case, observed at 41, gave a long history of disturbances in speech and gait, and athetotic movements. The demyelination of the white fibres of the globus pallidus in my two cases resembles somewhat the pathological picture seen in the cases described by Cécile and Oskar Vogt and others, but there is no clinical similarity.

Differentiation from other neurological disorders.—As seen from the clinico-pathological descriptions these two cases are closely related to Wilson's disease, pseudo-sclerosis of Westphal-Strümpell, chronic encephalitis, and amyotrophic lateral sclerosis with mental symptoms.

Pathologically, Case 2 showed a normal liver. In Case 1 the liver was not examined as permission for removal of the brain and spinal cord only was obtained. The absence of giant glia cells described by Alzheimer, and the lack of neuronophagia and glia rosettes, definitely rule out Wilson's disease and pseudo-sclerosis, but this differential diagnosis could not have been made clinically. The rapid course of the disease and the total absence of evidences of inflammation, in contrast to some of Jakob's cases which showed in places reactive inflammatory cells, would seem to rule out chronic encephalitis. These two cases were

considered at one time as amyotrophic lateral sclerosis with mental symptoms, but the pallidal symptoms would seem to exclude definitely this diagnosis. The pyramidal tract changes were most likely due to descending degeneration as a result of destruction of the giant pyramidal cells of Betz. In Case 1 the descending degeneration was only observed in the pyramids of the medulla oblongata and in the cortico-spinal tracts of the cord. A primary affection of these tracts, independent of the destructive changes in the giant pyramidal cells of Betz, must also be considered. The changes found in the anterior horn cells were possibly part of the disseminated process found elsewhere in the nervous system. Multiple sclerosis, although considered in these cases, as well as in those described by Creutzfeld and by Jakob, was definitely ruled out as the disease progressed. Pathologically the process was not at all related to multiple sclerosis.

IV.—SUMMARY.

A disease of comparatively short duration occurring in two adults without any demonstrable ætiology and presenting mental changes, pyramidal tract signs, absent abdominal reflexes and striatal symptoms, is described. Pathologically there was atrophy of the cerebral convolutions from the frontal to the parietal regions, scantiness and destruction of the ganglion cells in the third, fifth and sixth laminæ with areas of devastation, proliferation of glia and vessels, degeneration of the pyramidal tracts, calcification of the vessels of the pallidum, status demyelinated of the pallidal fibres, and changes in the anterior horn cells of the spinal cord. The name "disseminated encephalomyelopathy" is descriptive of the clinical syndrome and its pathology, but for the present it is advisable to adopt Jakob's title, Spastic Pseudo-sclerosis.

BIBLIOGRAPHY.

- [1] CREUTZFELD, H. G. Ueber eine eigenartige herdformige Erkrankung des Zentralnervensystems, *Zeit. f. d. ges. Neur. u. Psych.*, 1920, **57**, 1-19.
- [2] JAKOB, A. Ueber eigenartige Erkrankungen des Zentralnervensystems mit bemerkenswerten anatomischen Befunde, Spastische Pseudosklerose—Encephalomyelopathie mit disseminierte Degenerationsherden. *Ibid.*, 1921, **64**, 146-228.
Idem. "Spastische Pseudosklerose"; "Die Extrapyramidalen Erkrankungen," Berlin, 1923, 215-245.
- [3] ALZHEIMER, A. Ueber eine eigenartige Erkrankung des zentralen Nervensystems mit bulbären Symptomen und schmerzhaften Krampzuständen der Extremitäten. *Zeit. f. d. ges. Neur. u. Psych.*, 1916, **33**.
- [4] VON ECONOMO U. SCHILDER. Eine der Pseudosklerose nächstehende Erkrankung in Präsenium, *Ibid.*, 1920, **55**.

- [5] STAUFFENBERG. Cited by HALLEVORDEN in "Die Anatomie der Psychosen," Berlin, 1930.
- [6] WÖRCKM. Cited by HALLEVORDEN in "Die Anatomie der Psychosen," Berlin, 1930.
- [7] FLEISHACKER, H. "Afamiliäre chronisch-progressive Erkrankung des mittleren Lebensalters vom Pseudosklerosetyp," *Zeit. f. d. ges. Neur. u. Psych.*, 1924, **91**, 1.
- [8] KIRSCHBAUM, W. "Zwei eigenartige Erkrankungen des Zentralnervensystems nach Art der Spastischen Pseudosklerose (Jacob)," *Ibid.*, 1924, **92**, 175.
- [9] HURST, W. J. E. "On the so-called Calcification in the Basal Ganglia of the Brain," *Journ. Path. and Bact.*, 1926, **29**, 65.
- [10] HALLEVORDEN u. SPATZ. Eigenartige Erkrankung im extrapyramidal motorischen System. Ein Beitrag zu den Beziehungen zwischen Globus Pallidus und Substantia Nigra, *Zeit. f. d. ges. Neur. u. Psych.*, 1922, **79**, 254.
- [11] URECHIA, C. I. et ELEKES, N. "Syphilis des petits vaisseaux du cerveau," *L'Encephale*, 1923, **18**, 240.
- [12] LHERMITTE, J., KRAUS, W. M., and MCALPINE, D. "On the Occurrence of Abnormal Deposits of Iron in the Brain in Parkinsonism, with Special Reference to its Localization," *Journ. Neur. and Psych.*, 1924, **5**, 195-208.
- [13] SPIELMEYER. "Histopathologie des Nervensystems," Berlin, 1922.
- [14] BASSON, P. and HASSIN, G. "Calcification of the Cerebral Vessels with a Clinical Picture Simulating Brain Tumour," *Arch. Neur. and Psych.*, 1921, **6**, 359.
- [15] GYELEN, H. R. and PENFIELD, W. "Cerebral Calcification Epilepsy," *Ibid.*, 1929, **21**, 1020-1048.
- [16] HATFIELD, G. "Siderosis of the Globus Pallidus; its Relation to Bilateral Neurosis," *Journ. Path. and Bact.*, 1932, **32**, 135-149.
- [17] VOGT, C. and O. "Zur Lehre der Erkrankungen des striären Systems," Berlin, 1920.
- [18] FISCHER, O. "Zur Frage der anatomischen Grundlagen der Athétose double und der posthemiplegischen Bewegungsstörung überhaupt," *Zeit. f. d. ges. Neur. u. Psych.*, 1911, **7**.
- [19] ROTHMANN, M. "Demonstration zu den Zwangsbewegungen des Kindesalters," *Neur. Centralbl.*, 1915, **34**, 444.
- [20] KALINOWSKY, L. "Familiäre Erkrankung mit besonderer Beteiligung der Stammganglien," *Monatsh. Psychiat.*, 1927, **66**, 168.
- [21] FUNGFELD. "Zur Klinik und Pathologie frühkindlicher, das striäre System bevorzgender Erkrankung," *Journ. Psych. u. Neur.*, 1925, **40**, 85.
- [22] ONARI, K. "Ueber zwei klinisch und anatomisch kompliziert liegende Fälle von Status marmoratus des Striatum," *Zeit. f. d. ges. Neur. u. Psych.*, 1925, **93**, 457.
- [23] LHERMITTE et VON BOGAERT. Étude anatomo-clinique d'un cas de syndrome rigide avec spasme de torsion," *Rev. Neur.*, 1929, **36**, 941.
- [24] WINKELMANN, N. W. "Progressive Pallidal Degeneration," *Arch. Neur. and Psych.*, 1932, **27**, 1-21.

THE DIFFERENTIATION OF BEHAVIOUR PATTERNS IN THE FETUS AND INFANT.

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THE first appearance and development of behaviour patterns form an important subject for study with practical application as a basis for the understanding of the more complicated reactions of the adult. From the experimental point of view the problem offers considerable difficulties in the case of most mammals, inasmuch as the foetus must be removed from the uterus and observed under very artificial conditions where proper oxygenation of the blood is almost impossible. This latter objection applies especially to the study of the human foetus of the second to the sixth month where the umbilical cord must be severed before the observations are begun. Obviously the fundamental work must be done upon forms lower than mammals where the organism has an independent blood-supply from the beginning, or upon mammals which are born very immature after a short gestation period. The first of these methods has been used by Coghill, who formulated in this way general principles of behaviour development which appear to hold also for mammals. The second method has been used by the author, inasmuch as he obtained a very suitable mammal for study, the opossum.

Coghill was exceedingly fortunate in his choice of an experimental animal, *Amblystoma punctatum*, an example of the amphibian Urodela. In this form the tail is not absorbed in metamorphosis from the tadpole to the adult condition, but the trunk and tail continue throughout life as a flexible, integrated organ, the bending of which gives the animal its power of aquatic locomotion and subsequently becomes the primary factor of locomotion on land.

The opossum (*Didelphys virginiana*), a marsupial, is born after a ten-day gestation period, when scarcely more than one centimetre long. The young is able to crawl into the pouch by seizing the hair of the mother with the claws of the fore-leg and pulling itself along. The distance covered in this journey is, of course, short. When it has reached the pouch it seeks for and becomes attached to a nipple. The

nipple is swallowed far down in the pharynx and the young remains attached for weeks without relinquishing its hold. The movements of the animal in the pouch appear to be few, and certainly the field of activity is very circumscribed. At this time the skin, covered by no coat of fur, is pink and wrinkled, appearing too large for the animal; it is also thin and transparent, so that structures underneath are visible. The fore-legs are relatively large and muscular with well-developed claws; the hind-legs are mere buds and show very little differentiation. The tail is as long as the fore-legs. No vibrissæ are present on the face; the lateral mouth grooves have not developed and the mouth appears as a round hole. The eyes are not open, in fact no eye-slits have yet appeared. The pinna of the ear is just developing from the underlying skin. Inasmuch as the form of the body organs is not yet complete, these may be considered as embryonic preparations.

There remains to consider the observations of human foetal preparations made by Minkowski and others. Perhaps the total number of specimens studied is now over fifty. Minkowski was fortunate in that he was able to examine a number of foetuses removed at hysterectomy which was performed under local anæsthesia. The specimens were, therefore, not anæsthetized, and must have been much more active than those obtained at operation when a general anæsthesia is used. The foetus was immediately placed in a bath of physiological saline heated to 37° C.; observations could often be continued for as long as two hours. The umbilical cord was severed when the foetus was obtained, and the preparation must be considered as asphyxiated from the very beginning of the observations. However, it is permissible to accept the findings in so far as they agree with those obtained from other animals in which the oxygenation of the blood is more perfect. The discussion of the observations will be considered under topical headings representing general principles of development of behaviour patterns with the evidence obtained from the work just described.

Coghill showed that the first reflexes represent the total activity of the organism. The behaviour pattern from the beginning expands throughout the growing, normal animal as a perfectly integrated unit, whereas partial patterns arise within the total pattern and, by a process of individuation, acquire secondarily varying degrees of independence. In the development of the individual the earliest reactions are generalized, and it is only later that specific behaviour patterns develop out of this generalized reaction. Complexity of behaviour is not derived from the progressive integration of more and more originally discrete units.

Partial patterns emerge and tend toward independence and dominance, but always remain under the supremacy of the individual as a whole.

In the case of the amblystoma, this may be illustrated by the development of the reflex for progression. The first movements are made by the most anterior part of the muscle system of the trunk. They consist of a bending of the trunk to one side or the other. As the animal grows older, this flexion extends farther and farther tailward. These movements gradually increase in speed, and, in this way, acquire locomotor value. A flexion of the body in one direction followed by a flexion in the opposite direction produces swimming. When the legs have developed the primary component of walking is a slow, swimming movement of the trunk and tail which involves the limbs. The fore-legs are integrated with the movement of the anterior portion of the trunk, and the spread of the trunk movement to the region of the hind-legs involves them in movement. Accordingly, the hind-legs do not move synchronously with the fore-legs, but lag behind them by the interval required for the trunk flexure to spread from the fore-leg to the hind-leg.

Hartman (1920) observed and described the birth of the opossum. The adult female first showed signs of restlessness and began cleaning the pouch, which she did about four times. Then began a series of spontaneous contractions of the abdominal wall, after which she came to a sitting posture with legs extended, body bent forward, and began to lick the vulva. Suddenly a tiny bit of flesh appeared at the vulva and scampered up over the entanglement of hair into the pouch. Unerringly the embryo travelled by its own efforts; without any assistance on the mother's part, other than to free it of membranes and liquid on its first emergence into the world. This ten-day-old embryo is able, immediately upon its release from a liquid medium, to crawl a full three inches over a difficult terrain. Indeed, it can do more: after it has arrived at the pouch it is able to find the nipple amid a forest of hair.

The adult female was then etherized and the interior of the pouch examined. It contained a squirming mass of eighteen red embryos, of which twelve were attached, although thirteen might have been accommodated. The remainder were, of course, doomed to starvation. Some of these held on with their mouths to a flap of skin or the tip of a tail, while several continued to move about.

Hartman gently pulled off a number of embryos from the nipples. The teats had already been drawn out from about a millimetre in height to double that length, doubtless by the traction of the embryo itself.

One detached young, placed near the vulva, crawled readily back into the pouch. Two or three others regained the teats after some delay, while one wanderer found a vacant teat and attached itself after twenty minutes. If the skin be tilted, the embryos can be made to travel upward and even away from the pouch, for they are negatively geotropic. For locomotion the embryo employs a kind of "overhand stroke" as in swimming, the head swaying as far as possible to the side opposite the hand which is taking the propelling stroke. With each turn of the head the snout is touched to the mother's skin, and the embryo stops at once when the nipple is reached.

Goerling (quoted by Hartman) saw a new-born kangaroo clinging to the long hair about 4 in. below the opening of the pouch. It moved about very slowly, pushing its way upward through the hair. The head moved continually from side to side. Nearly thirty minutes were required for the little wanderer to reach the top of the pouch. During the whole of this time the mother paid no attention to her offspring, offering no assistance and leaving it to its own exertions.

Several young opossums, seven days old and 27 mm. in length, were removed by the author from the pouch for study. They were very active but helpless to cope with the environment outside the pouch. The opossums always lay on the side and never with the ventral surface of the body downward. The persistent flexion of the trunk prevented them from assuming this posture. The muscular contractions were widespread and consisted of contractions of the abdominal trunk musculature, causing a curving of the body with a bowing of the back. Beats of the fore-legs occurred but there was little contraction of the hind-leg musculature. It is evident that the first contractions of the musculature of the opossum involve the trunk and abdominal musculature and are very diffuse.

A pattern has, however, already grown out of this mass contraction of the body musculature, useful in that it enabled the animal to reach the pouch. If an opossum was placed upon a piece of gauze so that the claws could gain a hold, the claws of the fore-legs seized the threads and the young pulled itself along by alternate progressive movements of the fore-legs. The fore-leg contractions were not yet precisely coordinated units, but they were associated with contractions of the whole trunk musculature. The musculature was so strong that the young animal could support the weight of the body hanging by one fore-leg. It was only later, with the functioning of the vestibular mechanism, that the young animal could right itself upon a smooth surface and

remain with the ventral surface of the body downward. With the differentiation of the hind-legs their movements become co-ordinated with each other and with the fore-legs.

In the human foetus of two to six months the diffuseness of early motor responses is seen again. Minkowski found that it was not possible to obtain isolated reflexes but very generalized and variable motor reactions. For example, stimulation of the foot may produce, in addition to a withdrawal of the knee, motor reactions in both arms, the head and trunk. Stimulation in the region of the eye produced a contraction of the orbicularis muscle and movements of the legs in a foetus, 6.5 cm. in length.

Even the new-born human infant responds to stimuli with widespread motor responses which spread and increase in intensity with the strength of the stimulus. It is only later, as differentiation from the response of the organism as a whole, that refinement and delicacy of activity evolve.

The sensory field of the reflex and the field of motor response are at first diffuse. The first response of an amblystoma to any tactile stimulus is a contraction of the musculature of the opposite side of the trunk. Similarly, when the young opossum is placed upon a table for inspection, touch, heat or pin-prick serve to increase the widespread contractions of the body musculature.

This is particularly well illustrated by the development of the plantar reflex in the human foetus and infant. At first the field from which this reflex can be obtained consists of the entire leg, and the response is equally widespread, consisting of movements of the toes and flexion of the ankle, knee and thigh. The opposite leg may also take part. Gradually, with further development, the sensory field for the response becomes limited to the plantar surface of the foot and only the toes take part in the reaction.

The gradual limitation of motor and sensory responses is due to the development of inhibition in the nervous system. In early development an adequate impulse carried into the nervous system is diffused widely to all motor cells; later the pathway becomes limited. The early response is seen in the adult after transection of the spinal cord when the isolated segments have become active. Then a sensory stimulus applied to a portion of the body innervated by the isolated cord produces a mass contraction of all the musculature innervated below the lesion. The reflexes have lost their local sign and a sensory impulse spreads widely, giving a mass reflex. The inhibitory control of the brain has been removed.

Activity in the spinal cord first develops in the cervical portion and progresses caudally; in the brain it begins in the medulla and progresses in a cephalic direction. Coghill observed that the first movement of amblystoma in response to stimulation occurred in the cervical region and, with development, gradually the movement spread farther and farther caudally. The response was a contraction of the myotomes on the opposite side of the body producing a curvature of the body away from the point of stimulation. No response could be obtained until definite anatomical circuits had been laid down in the nervous system. The sensory neurones at an early period of development have no local reflex connection with the anterior horn cells of the same segments, but communicate with commissural fibres at the level of the fifth myotome which carry the impulse to the opposite side of the cord. Gradually commissural neurones are developed in more caudal segments.

The opossum shows reflex activity of the fore-legs which is well co-ordinated at a time when the hind-legs are relatively undifferentiated. It is much later that patterns of reflex activity appear in the hind-legs. It might be said, of course, that the case of the marsupial is unique among mammals in that precocious development of the fore-legs is required to enable the young to reach the pouch. In kittens also the fore-leg movements become co-ordinated before those of the hind-legs. Study of the anatomical development of the spinal cord, using myelination of nerve fibres as a criterion, shows that medullation begins in the cervical portion of the cord and continues in a caudal direction.

As regards the brain, maturation first occurs in the medulla in the areas controlling respiration, deglutition and the orientation of the body, and gradually spreads cephalad through the mid-brain, thalamus and cerebral cortex. This is demonstrated in the human foetus and newborn, using myelination as an index of maturation. The vestibular mechanism and associated structures in the medulla develop very early, and when they begin to function the organism becomes oriented in respect to the environment.

Reflex patterns arise within the picture of total activity of the organism. When the legs are first developed in amblystoma they function with the total reflex activity of the trunk musculature without any local reflex modalities of their own. Later patterns of activity involve the leg musculature alone. Thus, from and within the total activity of the organism, patterns of movement are laid down in restricted groups of muscles; these patterns are always subservient to the total activity pattern of the individual. The same phenomenon was

observed in the opossum. The first activity undoubtedly consisted of contractions of the whole trunk musculature producing the squirming and twisting movements in which the fore-legs participated. Later, the fore-legs developed more circumscribed and precise movements in which the claws seized the hair and alternate movements of the fore-legs pulled the animal along.

The differentiation of reflex patterns is also observed in the studies of the human foetus. Minkowski obtained a reflex on stimulation in the region of the mouth in a foetus of 3.5 cm. Opening and closing of the mouth were associated with movements of the legs; the reflex pattern involved the motor system from the level of the trigeminal nuclei to the caudal portion of the cord. Opening and closing of the mouth as a purely local reflex occurred in an infant of 21.5 cm. It would appear that the oral reflex in response to touch first appears as a part of a larger pattern of movement and only later is differentiated as a distinct reflex.

One of the first reflex patterns developed is the escape reaction. Coghill early observed that the first reaction of amblystoma has the qualities of an avoiding reaction. Thus, a stimulus applied to the body produces a strong contraction of the muscles of the opposite side; this reaction carries the organism away from the stimulated point. Escape reactions may be elicited early in mammals. Stimulation of the foot-pad of one hind-leg of the kitten produces withdrawal of that leg and withdrawal of both hind-legs if the stimulus is of considerable intensity. Perhaps the diffuse and rather violent movements of the foetal preparation may be considered escape reactions.

Many of the earliest reflexes to develop do not, in themselves, appear to be of value to the organism. The grasping and hanging reflex observed in the human new-born infant would appear to be of no value to the infant; it is believed to be a survival of a mechanism observed in many primates by which the young are able to hold to the hair of the mother and thus are carried safely. The tail of the opossum becomes prehensile and can even support the weight of the body a considerable time before the animal leaves the pouch.

In the human subject many of the earlier developed reflexes are soon completely inhibited. This is true of the grasping or hanging reflex and also of the sucking reflex. It would appear that they become incorporated in other more complicated reflex patterns. The grasping reflex is lost at the time when the infant begins to reach out voluntarily after objects placed within its reach. Under certain conditions, such

as intoxication with drugs, organic lesions of the brain or in the insane, the hanging reflex may again appear in adults. Similarly, the sucking reflex early becomes conditioned, but it may sometimes be demonstrated in the old or insane.

In amblystoma, a time occurs in development when the first response to sensory stimulation, the avoiding reaction, may be obtained. Coghill points out that this first response cannot be determined in its origin by previous responses, or modified by experience or exercise. The sensory pathways and their connections in the nervous system are laid down before the sense organ differentiates and functions, so that responses are limited to anatomical pathways already formed.

In order to understand the development and growth of behaviour patterns in mammals, it is necessary to account for their differentiation from the diffuse total pattern of activity before the birth of the animal. Bok's hypothesis of the circle reflex, particularly as elaborated by Holt, gives an explanation for the development of early specific reflexes.

First, it must be assumed that sense organs may be stimulated *in utero*, and that many sensory stimuli continually enter the central nervous system from proprioceptive endings in the muscle, from the skin and from certain special sensory organs. Indeed, in the case of the human subject, it is probable that all types of sense organs may receive adequate stimuli in the uterus except the olfactory and optic. The proprioceptive sensory apparatus is probably one of the earliest to function.

When a sensory stimulus enters the nervous system, it spreads widely and produces a diffuse motor response of the striated musculature. For an example, the biceps muscle contracts in this generalized response, involving also many other muscles. The contraction of the biceps stimulates the proprioceptive endings in the muscle itself, which in turn send impulses to the nervous system. Inasmuch as these sensory fibres have the closest anatomical relationship in the cord with the motor cells innervating the biceps, and inasmuch as the sensory impulses from the muscle reach these cells before the initial contraction is complete, the secondary influence tends to reinforce the first contraction. In this way a circle reflex is set up and becomes, in time, active continuously. Stimuli from proprioceptive endings in a muscle influence the anterior horn cells which continually send stimuli to the striated muscle. Throughout the life of the individual, tone in a muscle is dependent upon proprioceptive impulses arising continually in the muscle itself. If this reflex arc is broken on the efferent side, all tone is lost in the striated muscle.

The theory of the circle reflex may be used to explain the development of any of the early reflex patterns. Take, for example, the grasping reflex. Here the diffuse motor response may involve, in particular, the flexor musculature of the fore-arm and cause the fingers to press tightly against the palmar surface of the hand. Stimuli are then set up in the nerve-endings of the palmar surface of the hand or flexor surface of the fingers, both in superficial and deep structures, which tend to augment the contraction of the flexor muscles, inasmuch as the secondary stimuli reach the motor cells of the cord before the first contraction is complete. Thus a new circle reflex becomes established and any stimulation of the flexor surface of the hand produces the grasping reflex. With the development of function in the cortico-spinal pathway in the young infant, the grasping reflex is taken over by voluntary cortical control to be used in reaching and seizing objects. It is only under abnormal conditions that the primitive reflex again appears in adult life.

The first reflex patterns to develop, such as the reflex producing tonus in the muscles or the grasping reflex, are controlled by segmental or intersegmental reflex mechanisms. These reflexes are later modified, as has just been suggested, by influences from the brain; the tonus of an individual muscle comes under vestibular influence and becomes a part of a pattern of tonus, and the grasping reflex becomes a part of voluntary reaching.

Minkowski, in the case of the plantar reflex, has endeavoured to follow the development of control from different portions of the brain over segmental reflexes. The first stage he calls the embryonic or transition stage; it appears during the second month of foetal life. The reaction to stimulation of the dorsal surface of the foot is characterized by its inconstancy and variability. Sometimes a dorsal flexion of the toes occurs, followed by a plantar flexion. The reaction may be reversed during the course of the observation. It appears at a time when there is a transition from an ideomuscular response to a control of the muscle by the nervous system. The reflex through the nervous system is as yet inconstant and labile. The response is obtained only under particularly favourable conditions and after only a small proportion of the stimuli. Its form is determined each time by the state of excitability and conductivity of the corresponding segments of the cord.

The second stage of development is called the early foetal or spinal stage; it can be elicited in a foetus from 5 to 13 cm. in length, corresponding to the third or fourth month of foetal life. The dorsal flexion

of the toe predominates at this time over plantar flexion, but this predominance is only relative and is seen only under favourable conditions. During the course of the observation the extensor reflex may change to flexion. This response is believed to be controlled entirely by spinal centres and is uninfluenced by cutting the spinal cord in the cervical region.

The third stage is called the tegmento-spinal stage. The preparations in which this can be demonstrated are from 16 to 30 cm. in length and four to six months of age. At this period it is the dorsal type of response which predominates. The reactions show all the types of variation seen in the clinic, such as dorsal extension of the great toe alone, spreading of the toes or extension of the toes of the opposite side. Sometimes, after a period of the reflex in extension, plantar flexion is seen, with or without participation of the great toe; this is the phenomenon of inversion. At this period the great toe may not only flex but also oppose the other toes, giving the prehensile reflex which is found regularly in the monkey. Flexing of the whole leg may accompany extension of the toes.

This phase of the plantar reflex cannot be considered to be controlled entirely by the spinal cord but is dependent on supraspinal factors. Section of the cervical portion of the cord is followed by a transitory period of shock and of areflexia. Then a plantar type of response is frequently produced. The plantar reflex is now under the influence of a supraspinal factor which favours dorsal flexion; this control lies in the medulla. The reticulo-spinal tract and medial longitudinal fasciculus are now beginning to influence the activity of the anterior horn cells.

It is not proposed to consider the other four stages in the evolution of the plantar reflex which Minkowski described, ending with the control of this reflex by cortico-spinal influences in the normal child over 2 years old. This illustration suggests a method that may be used in further studies of the development of control by the brain over early segmental and intrasegmental reflexes.

Tonic and postural reflexes appear very early in the differentiation of the nervous system. Coghill observed that postural reflexes could be observed in the legs of the amblystoma before any isolated reflexes, apart from generalized movements with the trunk. The newborn opossum lies upon the side with the whole body flexed ventrally. Even at this time postural reflexes are active in the fore-legs, for if the claws are allowed to grasp the threads of a piece of gauze, the body can be

oriented in such a way that effective alternate movements of the fore-legs may occur.

Minkowski found that in the human foetus of two months, tonus in the musculature of the extremities maintained them in a determined position, and returned them to that position after they had been passively moved. Tonic reflexes produced by changes in the position of the head in relation to the trunk and labyrinthine reflexes were obtained from the foetus of the third or fourth month.

Graham Brown (1914) showed that, under certain conditions, even in adult life, the anterior horn cells of the cord may react to substances carried in the blood-stream after the manner of the respiratory centre. Herein lies the difficulty of observations upon foetal preparations after the umbilical cord has been tied and no respiratory reflexes are active. Asphyxia gives rise to diffuse motor stimulation.

It is also possible that the first motor reactions of the foetus occur in response to blood-borne stimuli. This implies that the motor side of the reflex arc becomes receptive before the sensory side. There is some slight evidence that the motor cells are mature before the sensory. In the spinal cord the motor roots are myelinated before the sensory. To use these data one does not need to assume that nerve fibres become myelinated at the time when they become functional, but only that fibres become myelinated in the order in which they become functional. Then activity would begin upon the motor side and the circle reflex develop with the first responses of the sensory portion of the reflex arc.

The first motor responses in response to sensory stimulation are diffuse. Anatomically, it is clear that the sensory neurones which enter the cord branch many times and establish countless numbers of reflex connections. By the mechanism of the circle reflex patterns of behaviour are developed. This implies that certain connections of the sensory fibre in the nervous system have become inhibited so that diffuse responses no longer occur. Inhibition in the caudal half of the spinal cord, even in adult life, is evidenced by the mass reflex which follows transection of the spinal cord in the thoracic region.

Pavlov believed that conditioned reflexes were all dependent on the cerebral hemisphere. Krasnogorski (1909 and 1913) has studied the development of conditioned reflexes in the child, and found that the mechanism for association does not appear until the second half of the first year, and is not functionally complete until the second year. He believes that associations are more readily extinguished in children than in dogs.

There is much evidence that conditioning occurs in the human infant at an earlier age. In the newborn, the sucking reflex is very active and may be obtained by placing the finger on the lips or even touching the cheek. Non-specific responses disappear during the first few weeks; the sensory area for sucking becomes specific for special types of lip stimulation. The child early becomes conditioned in respect to food. It will reach for the bottle by the one hundred and twentieth day and, even before that time, movements of the arms and legs are increased when the bottle appears. The functions of elimination can be conditioned from the second week on; it becomes a matter of only a little care to condition them after the third month.

Indeed, the development of the earliest reflexes of the foetus show many analogies with the conditioned reflexes. Gradually the sensory locus and the motor response become circumscribed and purposeful, due to the inhibition of disturbing extraneous factors. The mechanism of differentiation of all behaviour patterns does not differ from that effective in the production of the conditioned reflex.

BIBLIOGRAPHY.

- BOK, S. T. (1917). "The Development of Reflexes and Reflex Tracts," *Psychiat. en Neurolog. Bladen*, **21**, 287.
- Idem* (1915). "Stimulogenous Fibrillation as the Cause of the Structure of the Nervous System," *ibid.*, **19**, 292.
- BROWN, T. G. (1914). "On the Nature of the Fundamental Activity of the Nervous Centers, together with an Analysis of the Conditioning of Rhythmic Activity in Progression and a Theory of the Evolution of Function in the Nervous System," *Journ. Physiol.*, **48**, 18.
- COGHILL, G. E. (1926). "The Mechanism of Integration in *Amblystoma punctatum*," *Journ. Comp. Neur.*, **41**, 95.
- Idem* (1926). "The Growth of Functional Neurones and its Relation to the Development of Behavior," *Proc. Am. Phil. Soc.*, **65**, 51.
- Idem* (1929). "The Early Development of Behavior in *Amblystoma* and in Man," *Arch. Neurol. and Psychiat.*, **21**, 983.
- HARTMAN, O. G. (1920). "Studies in the Development of the Opossum *Didelphys virginiana*, V—The Phenomena of Parturition," *Anat. Rec.*, **19**, 251.
- HERRICK, C. J., and COGHILL, G. E. (1915). "The Development of Reflex Mechanisms in *Amblystoma*," *Journ. Comp. Neur.*, **25**, 65.
- HOLT, E. B. (1931). "Animal Drive and the Learning Process," Henry Holt and Co., New York.
- KRASNOGORSKI, N. (1909). "Ueber die Bedingungsreflexe im Kindesalter," *Jahrb. f. Kinderheilk.*, **69**, 1.
- Idem* (1918). "Ueber die Grundmechanismen der Arbeit der Grosshirnrinde bei Kindern," *ibid.*, **78**, 878.
- LANGWORTHY, O. R. (1924). "A Physiological Study of the Reactions of Young Decerebrate Animals," *Am. Journ. Physiol.*, **69**, 254.
- Idem* (1925). "The Development of Progression and Posture in Young Opossums," *ibid.*, **74**, 1.
- Idem* (1926). "Relation of Onset of Decerebrate Rigidity to the Time of Myelination of Tracts in the Brain-stem and Spinal Cord of Young Animals," *Contrib. to Embryol.*, No. 89, Carnegie Institution of Washington, **17**, 125.

- LANGWORTHY, O. R. (1927 a). "The Histological Development of Cerebral Motor Areas in Young Kittens Correlated with their Physiological Reaction to Electrical Stimulation." Contrib. to Embryol., No. 104, Carnegie Institution of Washington, **19**, 177.
- Idem* (1927 b). "Correlated Physiological and Morphological Studies of the Development of Electrically Responsive Areas in the Cerebral Cortex of the Opossum." Contrib. to Embryol., No. 103, Carnegie Institution of Washington, **19**, 149.
- Idem* (1928 a). "A Correlated Study of the Development of Reflex Activity in Fetal and Young Kittens and the Myelinization of Tracts in the Nervous System." Contrib. to Embryol., No. 114, Carnegie Institution of Washington, **20**, 127.
- Idem* (1928 b). "The Behavior of Pouch-young Opossums Correlated with the Myelinization of Tracts in the Nervous System," *Journ. Comp. Neurol.*, **46**, 201.
- Idem* (1930). "Medullated Tracts in the Brain-stem of a Seventh-month Human Fetus." Contrib. to Embryol., No. 120, Carnegie Institution of Washington, Publication **407**, 87.
- Idem*. "Development of Behavior Patterns and Myelinization of Nervous System in the Human Fetus and Infant." Contrib. to Embryol., No. 139, Carnegie Institution of Washington. (In press.)
- MINKOWSKI, M. (1920). "Réflexes et mouvements de la tête, du tronc et des extrémités du fœtus humain pendant la première moitié de la grossesse," *Compt. rend. des séances de la Soc. de Biol.*, **83**, 1202.
- Idem* (1921). "Sur les mouvements, les réflexes et les réactions musculaires du fœtus humain de 2 à 8 mois et leur relations avec le système nerveux fœtal," *Revue Neur.*, **37**, 11.
- Idem* (1921). "Ueber Bewegungen und Reflexe des menschlichen Fœtus während der ersten Hälfte seiner Entwicklung," *Schweiz. Arch. für Neurol. und Psychiat.*, **8**, 148.
- Idem* (1921). "Movimientos reflejos del feto humano durante la primera mitad del embarazo," *Trabajos de la Univers de Madrid*.
- Idem* (1922). "Ueber frühzeitige Bewegungen, Reflexe und muskulare reaktionen beim menschlichen Fœtus und ihre Beziehungen zum totalen Nerven- und Muskelsystem," *Schweiz. Med. Wochenschrift.*, 721 and 725.
- Idem* (1925). "Sur les modalités et la localization du réflexe plantaire au cours de son évolution du fœtus à l'adulte," *Extrait du Congrès des Médecins, Aliénistes et Neurologistes*.
- WEED, L. H. (1917). "The Reactions of Kittens after Decerebration," *Am. Journ. Physiol.*, **43**, 131.
- WEED, L. H. and LANGWORTHY, O. R. (1925). "Developmental Study of Excitatory Areas in the Cerebral Cortex of the Opossum," *ibid.*, **72**, 8.
- Idem* (1925). "Decerebrate Rigidity in the Opossum," *ibid.*, **72**, 25.
- Idem* (1926). "Physiological Study of Cortical Motor Areas in Young Kittens and in Adult Cats." Contrib. to Embryol., No. 87, Carnegie Institution of Washington, **17**, 89.

NOTICES OF RECENT PUBLICATIONS.

Reflex Activity of the Spinal Cord. By R. S. CREED, D. DENNY-BROWN, J. C. ECCLES, E. G. T. LIDDELL and C. S. SHERRINGTON.
Pp. 183. Oxford: Clarendon Press. 1932. Price 10s.

Some ten years ago Sir Charles Sherrington introduced a new technique to the study of reflexes, and already a large literature has arisen from the results yielded by it and the new interpretation of spinal reflexes thereby derived. The essential feature of this new technique is an instrument called the "Isometric Torsion Myograph," by which reflex muscular contraction can be measured quantitatively, and consequently the relative numbers of motor nerve-cells involved in different reflexes deduced. By improved electrical methods the rate of discharge of motor neurones can also be ascertained.

In a small volume Sherrington and four of his co-workers have summarized the present position of the subject, presenting the accumulated evidence upon which the newer conceptions are based, and defining the many technical terms which make the reading of any modern contribution to the subject very difficult for one unfamiliar with its development.

Since the publication of the "Integrative Action of the Nervous System" in 1906, the broad outlines of spinal reflex physiology there defined remain fundamentally unchanged. Knowledge more especially of the intimate details of central excitation and inhibition has deepened, and has been applied with considerable success to the elucidation of the postural reflexes underlying muscle tone, and with more confidence the physiologist speaks of nerve cells and their discharge rather than in broader terms of reflex response.

The means by which afferent impulses cause neurone discharge have been explored in a variety of ways. The series of nerve impulses which an anterior horn-cell discharges in the course of its activity, and the way this scheme is affected by natural condition, now rests on a working hypothesis of "the central excitatory state." At the anterior horn cell incoming afferents converge to bombard the cell surface with excitatory or inhibitory effect. The motor-cell does not discharge unless a certain threshold of afferent bombardment occurs. Large numbers of motor neurones are affected in every reflex, but only a proportion of them discharge, so that there are widespread "subliminal fringes" to each reflex, and the variable reinforcements of these form the basis of co-ordination. The way in which afferent impulses of light function mutually interact, and the consequent variations in the number of motor cells brought to discharge are described. The tendon-jerks record more faithfully the

fluctuations of the spinal centre than was ever suspected by those who at one time would have called the knee-jerk a muscular phenomenon and not a reflex. Although the rigorous fixation of the origin and insertion of the muscle by drill and clamps makes the isometric method impracticable for use in recording human reflexes, yet the elucidation of the stretch reflexes and their interactions explains many of the curious reflex phenomena in spastic patients.

The book has no pretensions as a clinical manual, nor does it attempt to describe reflex phenomena in man. The principles of reflex action are, however, of prime importance to those interested in clinical reflex changes.

Cytology and Cellular Pathology of the Nervous System. Edited by WILDER PENFIELD. New York: PAUL B. HOBBER. 1932. Pp. 1,267. (3 vols.) Price \$30.

This work is planned on the same lines as the well-known series of volumes on Cytology edited by Professor Cowdry, to which it may be considered supplementary. Its aim is to present a full and clear description of the various structures which make up the nervous system, including the peripheral end organs and the retina, and to give some indication of the alterations which they undergo in disease. As is to be expected in a work on cytology, normal appearances are more fully described than pathological changes; but this is an advantage to the neurologist, who is apt to be so attracted by the abnormal that he fails to obtain a thorough knowledge of the normal. It is true that a few chapters in the third volume are devoted entirely to pathological conditions, but these only attack a small sector of the field of neuropathology. The chapters on hydrocephalus and on tumours of the brain, the spinal cord and the eye are useful synopses of recent work. But undoubtedly the most valuable chapters are those in which the editor's own pioneer work is summarized. These have a strongly individual and often unorthodox bias which, to the reader, is always stimulating, albeit occasionally somewhat confusing. It has been the editor's object to include contributors of all nationalities and chapters have been written by Ariëns Kappers on neurobiotaxis, by Boeke on nerve-endings, by Bielschowsky on the histopathology of nerve-cells, by Nageotte on the peripheral nerves, and by Del Rio Hortega on microglia. These will ensure for the book a wide popularity. But many of the chapters contributed by American authors are not less important. Those by Cowdry on the neurone, by Penfield on the neuroglia, by Cobb on the cerebrospinal blood-vessels, and by Weed on the meninges are records of pioneer work of the highest value.

The high price of the book is explained and largely offset by the richness and excellence of the illustrations. Unfortunately the beautiful printing is marred by bad proof reading. Almost every chapter contains a gross printer's error, and in some they are to be found on nearly every page. We hope that a second edition may afford the opportunity of removing this blemish.

Handbuch der biologischen Arbeitsmethoden. Herausgegeben von E. ABDERHALDEN. Abt. V. *Methoden zum Studium der Funktionen der einzelnen Organe des tierischen Organismus.* Teil 7, Hft. 8, S. 995-1,073. Berlin: Urban and Schwarzenberg. 1932. Price 10 Rm.

Previous sections of this comprehensive laboratory handbook have been noticed in this Journal. The present volume contains chapters describing the investigation of tone appreciation, the investigation of labyrinthine functions in reptiles, amphibia, fishes and cyclostomes, and a chapter on the sensory functions involved in the method of palpation.

Hausmann, the author of the last-named article, has confined himself wholly to German sources in his review of the literature. No balanced statement of so difficult a subject can come from so arbitrarily circumscribed an outlook, and the article has therefore the limitations to be expected.

Intracranial Tumours. By HARVEY CUSHING. Pp. 150. Baltimore: C. C. Thomas. 1932.

At the recent meeting of the International Neurological Congress at Berne, Cushing presented a review of the percentage mortality of his operations on cerebral tumours, based on a series of 2,000 cases treated during the past thirty years, in which the natures of the tumours were verified by histological examination. This volume is an amplification of this presentation. The so-called "tumour-suspects," of which there were over 1,000, and cases in which the existence of a tumour was not confirmed by microscopical examination, almost as numerous, are not included in this summary. The tumours are classified according to their structure, the gliomata being subdivided into the types described by Bailey and Cushing, and each type is dealt with separately: in most instances a few case histories are published to illustrate their main clinical and surgical features. The histology of the growths is not described, but references are given to sources where the reader can easily find full descriptions.

But the main interest of this monograph lies in the results of operative treatment. These are carefully tabulated for each type of tumour, as well as for the whole series, for each of the thirty years which cover Cushing's work. As in many instances two or more operations were performed on the same patient, percentages are given separately for the case mortality and the operative mortality. These figures refer, however, only to the fate of patients during their stay in hospital, which averaged thirty-nine days; they deal therefore only with immediate mortalities following operation, and unfortunately give no information on the final results of surgical treatment. The author emphasizes the difficulty in following up and determining the fate of all patients, but it is regrettable that the later results of even a small number of unselected cases of each type are not furnished, for the ultimate prognosis is a

matter of much greater importance to the physician and to the patient than the risk of operation, and there are at present no adequate figures available to show what is the prospect of life in, for instance, the gliomas, by far the commonest of cerebral tumours. This side of the picture is at the most only hinted at, as by the confession that 100 per cent. of malignant gliomata end fatally, and that in astrocytomas for instance, recurrences may be expected within six to nine months.

But the most interesting feature of this monograph is the tables which show the gradual lowering of operative mortality during the past thirty years, which during the last ten years varied between 11 and 15 per cent., and in the last year under review fell considerably lower. The factors which contributed to this improvement are mentioned, but no detailed description of operative procedures are given in this book.

Spezielle Chirurgie der Gehirnkrankheiten. Von FEDOR KRAUSE.
Bd. 2. *Die epileptische Erkrankungen.* Part 2. Stuttgart:
Ferdinand Enke. 1932. S. 957. Price 63 Rm.

The previous volume dealing with the various clinical aspects of epileptiform seizures has already been noticed in a recent number of *Brain*. The present volume contains chapters devoted to the differential diagnosis of epileptiform seizures from hysterical and other seizures, to the aetiology of fits, and to the localizing diagnosis of focal brain lesions. It is, however, for the chapters dealing with the operative treatment of cases presenting epileptiform attacks that the work will be chiefly valued. Every aspect of cranial surgery is comprehensively discussed, the surgery of intracranial tumours and of traumatic brain lesions being equally considered, and the book will become a standard work of reference for neuro-surgeons. There are very numerous and excellent illustrations.

Beiträge zur Physiologie des Hirnstammes. I. Teil. *Die Methodik der lokalisierten Reizung und Ausschaltung subkortikaler Hirnschnitte.* Von W. R. HESS. S. 122. Leipzig: Georg Thieme. 1932. Price 24 Rm.

To Horsley and Clarke we owe the construction and employment of the first instrument of precision for the electrical stimulation of determined sites within the brain, and for the production of accurately localized, deep-seated, focal lesions. For the use of this stereotaxic instrument accurate maps of coronal and sagittal sections of the brains of the cat and of *Macacus rhesus* have been drawn up.

Horsley and Clarke used the instrument for investigations into the cerebellar nuclei, and subsequently Mussen in Baltimore and Barrington in this country have employed it.

However, the instrument is complicated and costly, and requires a high

degree of technical skill in its employment, and consequently it has not been so widely employed as its accuracy and usefulness deserve.

Professor Hess has sought to achieve the same end by a new and somewhat simpler apparatus, which is described in complete detail in his monograph, and he has drawn up an atlas of the cat's brain in conjunction with which it can be used. His method appears to have certain advantages of simplicity and ease of employment, but it is not possible for one who has not used both instruments to compare its accuracy with that of Clarke's stereotaxic instrument.

A Textbook of Neuro-anatomy. By ALBERT KUNTZ. Philadelphia: Lea and Fibiger. 1931. Pp. 359. Price \$5.50.

The value of a new textbook on the anatomy of the nervous system depends on its simplicity of presentation or its completeness for purposes of reference. In the present book the author makes no pretence to fulfil the latter criterion, claiming rather to have in view the needs of the student "in his first attempts to gain some knowledge of the anatomy and physiology of the nervous system." On the whole it succeeds fairly well, although its method is somewhat unorthodox. For example, the appearances of the spinal cord on external examination and on cross-section are described in Chapter II, its structural arrangement and cell systems in Chapter VIII, and the disposition of its tracts and fibre-systems in Chapter XII. The separation of the description of different constituents of the same organ may be justified on logical grounds, but its didactic value is doubtful.

While some chapters, for example that dealing with the cerebral cortex, have been brought well up to date, others, such as those on the cerebrospinal pathways, on the diencephalon and on nerve-endings are distinctly old-fashioned, and contain several statements which are contrary to modern teaching.

The book is fully illustrated, the best illustrations being borrowed from other textbooks. Of those that are original, the diagrams appear unnecessarily complicated and the photographs of the Weigert-Pal sections of the brain-stem are poorly reproduced from badly-stained sections, and show little that is not visible to the naked eye in fresh specimens.

Taken as a whole the book gives little that is not equally well presented elsewhere, and neglects many points that are of clinical significance.

La Syringobulbie. Contribution à la physiopathologie du tronc cérébral. Par N. JONESCO-SISBESTI. Pp. 391. Paris: Masson et Cie. 1932. Price 70 fr.

From his own large experience and from a comprehensive survey of the literature on the subject, the author describes the clinical features and the pathological characters of Syringobulbia. He brings out in his description many interesting points to which perhaps due attention has not been paid, as

the considerable proportion of cases in which the symptoms set in abruptly, or even in an apoplectiform manner, with headache, vomiting, vertigo, disturbances in articulation, phonation and deglutition; such acute attacks may recur in the course of any case. The description of the anatomical lesions is excellent and well illustrated.

But the most important section of this monograph is the analysis of symptoms and their correlation with such lesions as are found in syringobulbia, and the physiological deductions made from the symptoms observed. The diplopia which occasionally occurs is attributed to upset of the labyrinthine apparatus, hiccupping to irritative lesions of the subependymal vegetative nuclei, and the mental symptoms occasionally associated with the disease to disturbances of the neuro-vegetative centres of the bulb. Such conclusions may not be generally accepted, but the author's conclusions on the functions of the bulbar cranial nerves may be useful in stimulating a re-investigation of views which have been for long accepted as established.

Fleckfieber und Nervensystem. Von N. HIRSCHBERG. S. 124. Berlin: S. Karger. 1932. Price 11.60 M.

Though typhus fever has practically disappeared from Western Europe, the subject of this monograph is of interest at the moment in view of the nervous lesions which have occurred in recent outbreaks of other infections, as measles and smallpox. The author has had a large experience of this disease in Moskau, but unfortunately his book is mainly a review, and not always critical, of the literature of the nervous complications of typhus. He does not furnish any personal pathological observations and therefore fails to present a satisfactory discussion of the nature and cause of the various nervous symptoms which occur. The chapter on the pathological anatomy is merely a summary of old and more recent observations in which the reader receives no critical help from the author.

Les Troubles du Sommeil. Par H. ROGER. Pp. 206. Paris: Masson et Cie. 1932. Price 20 fr.

In his first chapter the author describes the special features and the nature of normal sleep, and the many theories which have been put forward to explain it; he assumes that the parasympathetic system, the cerebrospinal axis and mind acting together determine it. The second chapter deals fully with the varieties of insomnia and their treatment, and the third is devoted to the hypersomnias, which are divided into two classes, pathologically prolonged sleep and narcolepsy. But the final chapter on the various qualitative disturbances of sleep, included by the author in the term parasomnia, which are so often neglected by writers of textbooks and monographs, is perhaps the most interesting and important in the book. The lucidity of the style and the practical point of view from which it is written make the small monograph readable and useful.

Probleme der klinischen Psychiatrie. Von KURT SCHNEIDER. Leipzig : Thieme. 1932. S. 46. Price Rm. 2.60.

This is an admirably lucid, brief examination of the broad problems of clinical psychiatry. While so many consider the minute investigation of a particular aspect of psychopathology to be the only profitable study, this wide examination of the problem has especial value. An excellent instance of the author's attitude is in his temperate criticism of the doctrines of Kretschmer and of Kleist. The book is small, and is so interesting that most readers will finish it at a sitting and then return for closer consideration ; most of the tendencies in modern German psychiatry are reviewed in it with appreciative sharpness.

Constitution-Types in Delinquency. By W. A. WILLEMSE. With 32 plates and 19 diagrams. London : Kegan Paul. 1932. Pp. 266. Price 15s.

Dr. Willemse has examined a number of delinquent youths as to their physical and mental constitution, using in the main the methods and criteria of Kretschmer. He has endeavoured to bring into relation the attributes of the various types and the form of the delinquency. He has also attempted to co-ordinate the types delimited by Kretschmer with those of Jaensch and others. The author has read enormously rather to the detriment of his book, but as he is desirous of making these writers better known, the defect of readability which results from his indiscriminating citation may be a conscious and intentional failing. The investigation recorded has been carefully done, and the book contains a great deal of valuable material for the criminologist.

Das Retikulo-Endotheliale System der Schizophrenen. Von FR. MEYER. Berlin : Karger. 1931. S. 124. Price Rm. 12.

The search for somatic changes in schizophrenia is being actively pursued, and it occurred to Dr. Meyer that in the reticulo-endothelial system lay an important, and so far neglected, field of investigation. He used the congo-red test of Adler and Reimann, and Kaufmann's method which consists in examining the cellular content of the exudate in a blister. He applied these methods also to patients with other mental disorders than schizophrenia. His conclusions were that in schizophrenia during an attack the storage function of the reticulo-endothelial system is impaired, as is also its capacity to promote resistance to irritants ; disturbances in the activity of the liver cells and other metabolic disorders may be attributed to this. Somewhat similar findings were obtained in G.P.I., encephalitis lethargica and other psychoses. The work has been carefully done, but the interpretation of observations and the assumption that one is dealing with a primary rather than a derivative, unspecific phenomenon of the psychosis may be questioned.

Intelligence and Disease. By SHEPHERD DAWSON, assisted by J. C. M. CONN. London: Medical Research Council. 1931. Pp. 53. Price 1s.

The effect of illness upon the intelligence of children, as measured by the usual Binet-Simon tests, was investigated in Glasgow upon 1,000 children in hospital, healthy siblings being used as the material of comparison. Subsidiary studies on the relation of intelligence to stature were also made. The findings were that intelligence was unaffected by disease unless there were a more or less diffuse affection of the brain or of the ductless glands. It is surprising that in the work done on epileptics and encephalitics the effect of the drugs administered in these conditions does not seem to have been taken into account, particularly in regard to the results of retesting, which in the case of epilepsy are held by the author to indicate deterioration,

Baillière's Synthetic Anatomy. Part X.—The Brain. By J. E. CHEESEMAN. London: Baillière, Tindall and Cox. 1932. 12 plates. Price 3s.

These drawings resemble those already published of other parts of the body in being taken from sections in an oblique plane, the plane of one half of the brain and skull being less oblique than that of the other half. This arrangement shows more details of certain structures, but none the less adds to confusion. The more usual scheme of a series of sections in each of the three main planes is simpler and preferable. It is claimed, however, for the present sections that one obtains by one series a composite view for which at least two series in the usual planes would be necessary. It is no doubt possible to learn the gross anatomy of the brain and meninges from these drawings, and perhaps they have an additional value in that the difficulty in understanding them may serve to impress the details of the anatomy more deeply on the learner.

Histopathology of the Central Nervous System. By L. BOUMAN and S. T. BOX. Utrecht: A. Oosthoek's Publishing Co. 1932. Pp. 38, with 53 full-page plates. Price 25 florins.

In this atlas the authors have "tried to give a general survey of the histopathology of the most important diseases of the central nervous system by means of a series of micro-photographs accompanied by a short concise text." Such a method of presentation of neuropathology has definite advantages, and no less obvious defects; and within its limitations the authors have succeeded remarkably well. The photographs, which form the main part of the book, are clearly reproduced on stiff boards and should thus be of permanent value. The letterpress, although more concise than is necessary, gives clear and up-to-date descriptions of the different types of cell and their alterations in disease. The table, in which the lesions of the various inflammatory diseases of the central nervous system are contrasted, should be of special value to those with

a limited experience of these conditions. But also some amplification would have been valuable: for example, encephalitis lethargica is described as affecting chiefly the mid-brain, and little or nothing is said about the lesions which it produces in the cerebral hemispheres or the lower levels of the brain-stem.

We cannot suppress a regret that the authors did not make more generous use of their wide knowledge of neuropathology by considerable enlargement of the letterpress. Any slight increase of price which this would have entailed would certainly have been more than compensated by the increased value of the book. But as an atlas of the pathological histology of the nervous system the book is distinctly successful, and should have a definite value for those who wish to make a rapid survey of this field.

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EDITOR.

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NEUROBLASTOMAS AND GANGLIOCYTOMAS OF THE CENTRAL NERVOUS SYSTEM.

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TUMOURS composed of neuroblasts and ganglion cells form a well-recognized group. Most commonly they are found in the sympathetic nervous system, but they occur in the central nervous system with a frequency sufficient to warrant this study. They are not limited to any particular region of the brain or of the spinal cord, occasionally they are encapsulated and enucleable, but more frequently they are infiltrative and simulate gliomas. We shall review the clinical histories of nine such cases, consider their treatment, and describe the histological appearances of the various tumours. Seven of these were found in the cerebrum, and two in the substance of the spinal cord. The latter have been briefly mentioned in a previous study on intramedullary tumours of the spinal cord [6] and one of those in the brain has been described elsewhere [5] because of its association with diabetes insipidus; to complete our study, they have been described here in detail.

In a recent paper on this type of tumour Courville [4] reviewed the literature up to 1930, and as no further contributions have been brought to our notice it seems unnecessary to repeat his excellent summary. A detailed histological description will be given of the tumour found in

¹ Formerly in the Section on Neurology of the Mayo Clinic.

our first case; the remaining tumours in our collection will be compared with this, and their chief variations elaborated.

REPORT OF CASES.

In Case 1 there was a history of: (1) increasing intracranial tension for five weeks; (2) choked discs, with homonymous hemianopsia and partial loss of sense of position; (3) enucleation of neuroblastoma of left temporo-parietal area; (4) six years later, partial removal of recurring tumour, now gangliocytoma; and (5) death after four months.

Case 1.—A girl, aged 16, was brought to the Mayo Clinic on July 16, 1925, chiefly because of headaches. Five weeks previously she had begun to have severe bilateral fronto-occipital headaches early in the morning. About the same time she noticed that she saw double on looking to the right or left, and that she tended to bump into objects on her right. Three days previously she was found in a generalized convulsion.

The patient was well developed and well nourished, but her intelligence and co-operation were poor. The ocular movements were not restricted; horizontal nystagmus to both sides was easily elicited. The pupils were equal, dilated, and reacted sluggishly to light and in convergence. There was acute bilateral choking of the optic discs, measuring 5 diopters, and many hæmorrhages and patches of exudate were present in the retinæ of both eyes. Perimetric fields showed right homonymous hemianopsia. The neck was a little stiff. Moderate loss of the sense of position could be demonstrated in the right index finger and right great toe, and there was some inco-ordination of both the right arm and the right leg. When the patient walked slight ataxia was apparent in the right leg.

At operation on July 24, 1925, a tumour was found involving both the left temporal and left parietal lobes. It was approximately spherical and measured 3 cm. in diameter. In its interior was a cavity containing about 20 c.c. of yellow gelatinous fluid, which coagulated on standing. The growth involved the cortex, and was easily enucleated. Convalescence was uneventful, and the girl returned to her home a month later.

On May 20, 1926, the patient returned for re-examination. Vision was $\frac{20}{80}$ in both eyes. The pupils, pupillary reflexes, and ocular movements were normal. The optic discs showed the pallor of secondary optic atrophy. The homonymous hemianopsia had been replaced by bilateral cæcocentral scotomata. Neurological examination revealed no other changes.

According to a letter dated September 19, 1930, the patient was normal except that her vision was still impaired. She returned to the Clinic on March 5, 1931, complaining of bulging under the cranial scar, and of generalized muscular pain.¹ On March 12 an incision was made into the scalp through

¹ This may have been due to spinal metastases. See recent paper by Cairns and Russell [3].

the posterior limb of the original wound. A pulpy, granular tumour prolapsed; part of this was removed. After the patient returned to her home she was better for three months, but on July 5, 1931, she suddenly became comatose, and died four days later.

Microscopical examination (figs. 1 and 2)—The tumour removed in 1925 was markedly different from that removed six years later. The differences are best crystallized by comparing the stroma and the cells of one tumour with those of the other.

The stroma of the tumour removed in 1925 contained very little adult or hyaline connective tissue, but fibroblasts were numerous, especially toward the edge of the tumour and in the adjacent cerebral tissue, where many astrocytes and some spongioblasts were also to be found. In one part of the surrounding brain small masses of calcium were present, precipitated especially in the walls of arterioles, frequently on astrocytes, and occasionally on ganglion cells: in this area there was an excessive number of fibrous astrocytes. In the interior of the tumour only a few microglial cells, an occasional scavenger cell, and a number of diffusely arranged lymphocytes were present. The walls of the blood-vessels were thickened by proliferation of endothelium, which was occasionally sufficient to occlude the lumen; associated with these occluded vessels were many areas of necrosis surrounded by polymorphonuclear leucocytes. Occasionally the perivascular connective tissue was also increased; vessels so affected resembled those found in any spongioblastoma multiforme.

The stroma of the tumour removed in 1931 contained an abundance of connective tissue; some of its heavier bundles had undergone hyaline degeneration; although for the most part adult in type, this tissue was loose in texture. A certain amount of less mature connective tissue was also present; this contained well-differentiated fibroblasts. These did not stain bright red with the fuchsin of van Gieson's stain; compared with the cells of adult connective tissue, their nuclei were larger, more oval, and contained more chromatin, and their fibrils were shorter and heavier. The walls of the blood-vessels were normal; in many perivascular spaces lymphocytes were present, sometimes to excess. Lymphocytes were also found both diffusely throughout the tumour and occasionally collected in islands.

Most of the cells of the 1925 tumour were round or oval, a few were bipolar, and an occasional larger cell was polygonal. The dendrites arising from these cells were short and rudimentary. Only the polygonal cells contained Nissl substance, which was arranged in very fine granules around the periphery of the cell, and in its dendrites. In spite of the absence of Nissl substance from the smaller cells, the common origin from neurogenic tissue of all the cells of the growth was clearly indicated by their affinity for silver, and by the configuration of their nuclei. These were large, round and vesicular, and each contained a central deeply staining nucleolus. They were unusually eccentric, and lay close to the wall of the cell, or at one end of the unipolar and bipolar cells. Rarely one cell contained two nuclei, but never more than two, mitotic figures were numerous. The cells were readily impregnated with silver;

those axones which were so stained did not arise from the cells of the tumour, but from cerebral cells which had been included by its invasion.

The cells of the 1931 tumour, though not numerous, could be demonstrated by the toluidine blue stain in all parts of the growth. They had a tendency to grow in groups surrounded by connective tissue, but many single cells could be found. Most of the cells had fairly distinct outlines. They had three, four, or five sides, with a corresponding number of dendrites. The latter varied in size; the majority were relatively short and had broad bases, but occasionally larger dendrites were present. Some bipolar cells were to be found; these had heavy processes, tapering from both ends into the surrounding tissue. The cytoplasm of the cells was abundant, and frequently contained small vacuoles. It did not stain uniformly; many deeply staining chromatin granules were present, arranged diffusely throughout the cytoplasm and in the dendrites. In certain cells these granules were larger and more prominent, and were collected beneath the boundary of the cell; in these cells fine tigroid granules were present around the nucleus. Mitotic figures were absent. Sections impregnated with silver confirmed the appearances seen in those stained with toluidine blue; the characteristic nuclei were well demonstrated. Usually they were central in position; occasionally they were eccentric, and lay close to the cell boundary, but without causing any bulging of this.

The 1925 tumour was classified as a neuroblastoma; the 1931 tumour as a gangliocytoma.

In Case 2 there was a history of visual hallucinations, and progressive hemiplegia and aphasia for one year. Homonymous hemianopsia was present. Generalized convulsions, increasing weakness, coma and death resulted. Necropsy revealed a gangliocytoma of the left temporal lobe.

Case 2.—A man, aged 55, was brought to the Clinic on November 27, 1919, because of increasing weakness of the right half of the body, and of difficulty in expressing himself. One year previously a "red ball" suddenly appeared before the patient's right eye; he fell, and was unable to rise for ten minutes. Similar, although milder, seizures recurred a month later, and at irregular intervals thereafter. Four months previously the right leg began to drag, and this disability gradually became more marked. Two months previously the right hand became numb, stiff and slow. Four days before his arrival the right-sided weakness increased rapidly. One month previously he began to have increasing difficulty in expressing his ideas in words.

The blood-pressure in millimetres of mercury was 106 systolic and 75 diastolic. Visual acuity was 6/10 in both eyes. The pupils were equal, and reacted promptly to light and in convergence. Ophthalmoscopic appearances were normal. Almost complete right homonymous hemianopsia was present. The patient was markedly aphasic, and hemiplegia was almost total on the right side. Cerebrospinal fluid obtained by lumbar puncture was clear and colourless, but under increased pressure. On the day following the lumbar

puncture the hemiplegia was found to be complete; on the same evening the patient became comatose and died.

Necropsy.—The brain presented the usual signs of increase in intracranial pressure. Occupying chiefly the left temporal lobe was a tumour 4 cm. in diameter, poorly demarcated from the surrounding brain. The growth extended upward into the adjacent part of the parietal lobe and mesially into the cerebral peduncle; it compressed and lengthened the part of the left optic tract posterior to the chiasm. Much of its substance was necrotic and consisted of hæmorrhagic gelatinous debris. The lateral ventricles were not dilated, nor did the growth invade the left ventricle.

Microscopical examination (fig. 3).—The stroma of the growth was sparse and oedematous. The blood-vessels were well formed; endothelial proliferation was absent. Occasionally lymphocytes were found, but only in the perivascular spaces. The tumour was cellular; the cells varied much in size, and had a tendency to grow in groups rather than diffusely. Stained by toluidine blue, the majority appeared pyramidal or polygonal in outline, but many bipolar and unipolar cells were also present. In the pyramidal and polygonal cells the cytoplasm was more abundant, and occasionally vacuolated. Fine tigroid granules were present in the cytoplasm, and in some cases they had collected beneath the cell-boundary into larger masses; the few dendrites which were present contained a similar finely granular substance. The dendrites were not so sharply demarcated as in normal adult cells, but had broad bases, and short and indefinite outlines. The bipolar and unipolar cells stained a more uniform pale blue, and had few granules in their cytoplasm. The cells of the tumour had an affinity for silver, which outlined their bodies and dendrites; axis-cylinders were not observed. All the cells of the growth had characteristic nuclei; these were large, round and vesicular, and contained little chromatin except a prominent deeply-staining nucleolus. They were large in comparison with the size of the cell, and usually were situated in the middle of the cell-body, although occasionally they were eccentric. Cells more immature than the bipolar stage of neuroblasts were not identified and mitotic figures were absent.

This tumour was classified as gangliocytoma.

The history in Case 3 was of mental deterioration for six months; acute exacerbation of increase in intracranial pressure, coma and death. At necropsy a gangliocytoma of the left frontal lobe was found.

Case 3.—A physician, aged 39, was brought to the Clinic on July 6, 1920, in a semi-stuporous condition. Six months previously he began to lose interest in his professional work and in his home life, and three months later his condition progressed to drowsiness, and considerable stupor for the greater part of the time. Three weeks previously he began to have left-sided supra-orbital headaches, which occasionally radiated to the occiput and were associated with diplopia. Two weeks previously projectile vomiting appeared, and at the same time his speech became confused.

The patient was only semiconscious and much reduced physically. The blood-pressure was 132 systolic and 80 diastolic; the pulse-rate [42] was consistently slow. The pupils were equal in size, and reacted to light and in convergence. Both optic discs were swollen, the right to a height of 1 diopter, the left to 2 diopters. It was thought that the patient's general condition was too poor for even decompression to be considered; the following day he died.

Necropsy.—The brain was dry, and its convolutions were greatly flattened. The left frontal lobe was larger than the right, the mesial surface of which it indented. Occupying the enlarged lobe was an extensive, poorly defined tumour, the central part of which was necrotic. Macroscopically the tumour extended from the tip of the frontal lobe to the frontal operculum and to the posterior ends of the superior and middle frontal convolutions.

Microscopical examination (fig. 4).—Little stroma was present; the tumour was highly cellular. The walls of the blood-vessels were thin, and showed endothelial proliferation with mitosis; frequently the proliferation had led to obstruction of the lumen, and so to the formation of areas of necrosis. Lymphocytes and polymorphonuclear leucocytes were abundant around these areas, and the former were numerous around the blood-vessels.

On the whole, the cells of the tumour grew diffusely, although occasionally they were collected into clusters; they varied greatly in size. The majority were polygonal, and contained finely granular Nissl substance. In spite of the preponderance of adult cells, mitotic figures were numerous in less differentiated cells. The cells had an affinity for silver, which outlined their bodies and dendrites; axis cylinders arising from the cells of the tumour could not be demonstrated. The nuclei were characteristically large and vesicular, and contained central deeply staining nucleoli. Most of the nuclei were eccentric and lay under the cell membrane; many of these were oval. Some cells were swollen; the central part of these stained lightly with toluidine blue, and the periphery contained definite Nissl granules; in such cells eccentric nuclei were commonly found. It was impossible to demonstrate spongioblasts or astrocytes in the depth of the growth, but at its margin normal and degenerating astrocytes were identified.

This tumour was classified as a gangliocytoma containing many neuroblasts.

The history in Case 4 was of progressive loss of vision, diabetes insipidus, and hypopituitarism for two years. The region of the chiasm was explored, following which the patient died. Necropsy disclosed a gangliocytoma of the third ventricle.

Case 4.—A girl, aged 18, was brought to the Clinic on October 10, 1927, because of headache and progressive loss of vision. Two and a half years, previously she began to pass large quantities (4 litres in twelve hours) of almost colourless urine which did not contain sugar, and at the same time

she suffered from excessive thirst. A diagnosis was made of diabetes insipidus. This persisted for two years, during which she steadily gained in weight until she weighed twice as much as her normal. Most of the time she was drowsy, but she remained at school and made fairly satisfactory progress. Four months before her examination she began to complain of dimness of vision, which steadily progressed, so that after two months she often collided with people and objects. Two months previously she began to have dull pounding right frontal headaches; these occurred daily. About the same time she began to lose weight, and thereafter she was subject to occasional attacks of weakness, during which she perspired profusely. For several days before her arrival she was very weak, and spoke in a peculiar slurring manner.

The girl was well developed and well nourished, being 142 cm. tall and weighing 43.1 kg. The blood-pressure was 98 systolic and 64 diastolic. The patient slept in a drowsy stupor most of the time, but occasionally complained of pain over the right eye; nausea accompanied the pain, and sometimes she vomited. She was able to see large objects, but was unable to read even the largest print. The left pupil was somewhat larger than the right; both reacted promptly to light and in accommodation. The optic discs were full and pale. Perimetric examination disclosed right homonymous hemianopsia. In other respects, neurological examination was negative. In roentgenograms of the head the sella turcica appeared to be normal. There was no serological evidence of syphilis.

At operation the region of the optic chiasm was approached by elevating the left temporosphenoidal lobe. Evidence of a tumour in or about the chiasm was not detected. The patient withstood the operation poorly, and died twelve hours afterwards.

Necropsy (fig. 5).—The exterior of the brain did not show any sign of increase in intracranial pressure. A tumour was found in the lower and anterior part of the floor of the third ventricle, destroying the tuber cinereum and corpora mammillaria. The growth compressed lightly the infundibulum and hypophysis, but did not invade either. Anterior to the infundibulum the tumour had transgressed the floor of the third ventricle to invade the optic chiasm and posterior parts of the optic nerves; tumour tissue was also found in both optic tracts, especially in the left. The lateral walls of the third ventricle were little involved. The anterior part of the tumour had extended between the frontal lobes, without invading either. The growth as a whole had not interfered with the flow of cerebrospinal fluid. It was not sharply demarcated from the surrounding brain; it contained several small cysts, and a larger one anterior to the left optic thalamus.

Microscopical examination.—Sections of the optic chiasm stained by Weigert's myelin sheath method showed that much of its structure had been destroyed by tumour cells, so that myelin sheaths were absent. Tumour tissue could not be found in sections of the infundibulum and of the hypophysis. In the growth itself many lymphocytes and plasma cells were present, especially in the areas of cystic degeneration. The majority of the blood-vessels had thin

walls, the lining endothelium of which was proliferating and even contained mitotic figures. Throughout the tumour only a few astrocytes were found, but there were many in the adjacent brain tissue. The predominating tumour cells were of a type intermediate between neuroblast and gangliocyte; some of these were round cells without processes; others had one, two, or several processes. In many such cells mitotic figures were present. Almost mature ganglion cells were also to be seen, these had varying numbers of processes and contained immature Nissl granules. All the cells of the growth had the characteristic large, round, vesicular nucleus, with its central deeply staining nucleolus; cells containing two or more such nuclei were uncommon.

This tumour was classified as a gangliocytoma containing many neuroblasts.

The history in Case 5 was of loss of vision and progressive signs of internal hydrocephalus for six months. Ventricular estimation and ventriculography were carried out. The patient died following operation. Necropsy revealed a gangliocytoma of the third ventricle.

Case 5.—A man, aged 23, was brought to the clinic on March 18, 1931, because of loss of vision. Six months previously vision in the right eye had failed suddenly, and one month later that of his left eye also had failed. Four months previously he began to have headaches in the frontal region, and two months later these began to be associated with projectile vomiting. Two weeks previously he complained of abnormal sensations in the left hand, and evidence of blunting of intellectual and emotional faculties appeared.

The patient was well developed and well nourished. His co-operation was so poor that examination was difficult. The right pupil was larger than the left, and its reflex to direct light was markedly diminished. Ophthalmoscopic examination showed acute choking of both optic discs to a height of three diopters, with retinal hæmorrhages and exudates. Apparently he was blind in his right eye, but perimetric fields could not be obtained. Stereoscopic roentgenograms of the skull revealed convolutional atrophy of its inner table, and erosion of the sella turcica. A rapid, fine tremor of both hands, of both static and kinetic types, was present. Three days after his admission to hospital he had a generalized convulsion. A diagnosis was made of internal hydrocephalus, due to unlocalized tumour.

On March 24, 1930, ventriculography was performed. Ventricular punctures revealed bilateral hydrocephalus. The ventriculograms indicated that the lesion was a tumour involving the third ventricle. On the second post-operative day the patient died suddenly of respiratory failure.

Necropsy (fig. 6).—Signs of extreme increase in intracranial pressure were marked. The brain was dry and its convolutions were flattened. Numerous dural herniations were present, especially on the floor of the middle fossæ. The uncinate gyri, the gyri recti and the olfactory tracts were grooved as a result of pressure on the edges of the tentorium and on the olivoid processes. Both lateral ventricles were considerably dilated. In the lower half of the

anterior horn of the left lateral ventricle was found a greyish, cystic, hæmorrhagic tumour. Mesially this was attached to the left side of the septum pellucidum, anteriorly it extended into the head of the left caudate nucleus, and posteriorly it invaded the left optic thalamus. A small part of the growth eroded the septum pellucidum and appeared in the right lateral ventricle. The posterior part of the tumour occluded the left foramen of Monro, and displaced the septum pellucidum to the right so as to occlude the right foramen of Monro. On the lateral wall of the anterior horn of the right lateral ventricle was a small grey nodule, 5 mm. in diameter, which had an appearance and consistence similar to that of the main mass of tumour.

Microscopical examination (fig. 7).—The main tumour was highly cellular, although its blood-vessels had well-formed normal walls. Little stroma was to be seen, and astroblasts, astrocytes and spongioblasts were absent. The cells of the tumour were unusual in that they had some of the characteristics of astroblasts: large, homogeneous, eosin-stained cell bodies and eccentric nuclei. Stained with toluidine blue, the cytoplasm of certain of the cells was almost homogeneous, especially in the middle; in some cells small Nissl granules were collected around the periphery, in others small granules were scattered diffusely throughout their cytoplasm, and large granules were collected around the periphery. In sections impregnated with silver few cell processes could be identified, but often one end of a cell displayed an indistinct frayed outline like a fish's tail; axis-cylinders could not be demonstrated. The nuclei were typical; they were large, round, and vesicular, and each contained a deeply staining central nucleolus. Multinucleated cells were not observed.

This tumour was classified as a gangliocytoma. The small tumour on the lateral wall of the right lateral ventricle was an astroblastoma (fig. 8).

The history in Case 6 was of generalized convulsions and change in personality for eighteen months. A parasagittal gangliocytoma was removed, and the patient recovered.

Case 6.—A woman, aged 36, came to the clinic on August 27, 1927, because of attacks of generalized convulsions and failure of vision. Eighteen months previously she had had a sudden generalized convulsion which lasted for two to three minutes. After recovering from this she was dazed and went to bed; during the same day she had two similar attacks. After these convulsions a persistent weakness of the muscles of the left side of the face was noted. A week later she returned to work. Thirteen months previously she had another convulsive attack, which was followed by a feeling of weakness so marked that she stopped work; three months later she had another convulsion. Six months previously she began to have dull bitemporal headaches once a week. Each headache lasted one to three hours, and they persisted for three months, when they were replaced by severe stabbing pain in the temples and eyeballs. At this time the patient had a good deal of nausea, but practically never vomited. Three months previously her vision

began to fail and she had occasional diplopia. After her first convulsion a change in personality appeared; she became irritable, lost interest in her household and wanted to stay at home to be left alone.

Vision in the right eye was $\frac{2}{3}$ and in the left eye $\frac{1}{4}$. Both optic discs were swollen to 4 diopters. Perimetric fields showed concentric contraction for form and for colours, with enlargement of both blind spots. Weakness of the left side of the face was present. The tendon reflexes were more active on the left side of the body, but the left plantar reflex was flexor in type. A roentgenogram of the skull revealed, in the right frontal area, enlarged channels for diploic veins. A diagnosis was made of tumour involving the right frontal lobe.

On September 7, 1927, this region was explored. A tumour was found attached to the dura mater over the middle frontal convolution. It was smooth, round and indented the brain without invading it. Because of loss of blood from the large sinuses in the bone, the operation was divided into two stages. Nine days later the wound was reopened and a second bone flap turned down to the left side across the superior longitudinal sinus. The growth, which measured 15 by 18 cm., invaded the longitudinal sinus and appeared on the left side as a mass measuring 3 to 2 cm. It appeared to be encapsulated, and was, so far as could be determined, completely removed.

The patient had an uneventful convalescence. She was examined again in January, 1929, when she was in good physical condition. The only remaining sign of her illness was secondary optic atrophy, this had given rise to inferior nasal hemianopsia in the left eye, and inferior altitudinal hemianopsia in the right eye. Toward the end of July, 1929, she returned because she had had a convulsion. For some time her memory had been impaired, and occasionally her mind wandered. Further operation was not advised.

Microscopical examination (figs. 9 and 10).—The growth was similar to that found in Case 5. The blood-vessels had well-formed normal walls, and there were no extensive areas of necrosis. Lymphocytes were absent, and only around the blood-vessels was any connective tissue demonstrable. The tumour cells were large. They contained finely granular Nissl substance, which was often collected into larger granules under the cell membrane. No well-formed dendrites were present, although each cell had a frayed termination at one end. The nuclei were characteristically large, round and vesicular, and contained deeply staining nucleoli which were often eccentric; occasionally giant nuclei containing two nucleoli were present. Binucleated cells were common, and occasionally multinucleated cells were observed, but mitotic figures were absent. The silver stain did not impregnate any axis-cylinders. Some of the cells of the growth were undergoing cystic degeneration, so that many small cavities outlined by a delicate membrane were present throughout the tumour. Most of these cysts were empty, but a few contained homogeneous material which stained with both eosin and toluidine blue. The stages in the formation of these cysts from swollen degenerating tumour cells could be followed. Cysts of this type are almost always present in gangliocytomas arising from

the sympathetic nervous system, but this tumour was the only one in our series in which their occurrence was observed.

The tumour was classified as a gangliocytoma.

In Case 7 the history was of increasing intracranial pressure for five months, and homonymous hemianopsia and hemiparesis. A gangliocytoma of the right parietal lobe was partially removed.

Case 7.—A woman, aged 39, came to the Clinic on July 13, 1931, complaining of headaches and drowsiness. Five months previously she began to complain of occasional aches in the right fronto-temporal region; these gradually became more frequent and more severe, until after two months they occurred daily, for periods of three to twelve hours. Following this the headaches became more moderate; their evolution was always fairly constant; first a feeling of "coldness" was noted over the right fronto-temporal region, then dull pain and lastly sharp pain. The most severe headaches were associated with giddiness. Three months previously, when the headaches were at their worst, the patient became so drowsy that she slept most of the time and was unable to do her housework; at times it was impossible to rouse her. After two months she became less sleepy. Two weeks before her examination she complained of general weakness and of difficulty in walking.

The patient was well developed and well nourished. Vision was $\frac{5}{6}$ in both eyes. The pupils, pupillary reflexes and fundi were normal. Perimetric fields disclosed complete left homonymous hemianopsia. There was no roentgenological evidence of intracranial disease. Neurological examination disclosed moderate weakness of the whole left side, with a corresponding diminution of speed of movement and exaggeration of the deep reflexes. On the left side the superficial abdominal reflexes were diminished and the great toe responded by extension to stimulation of the sole of the foot. Sense of position was moderately decreased in the left index finger and markedly reduced in the left great toe. Some inco-ordination of the left arm and left leg could also be demonstrated. A diagnosis was made of tumour of the right parietal lobe.

At operation the convolutions in this area were found to be of a firm, rubbery consistence. The tumour, which extended deeply into the white matter, was partly extirpated with the electro-surgical unit. The patient made an uneventful recovery.

Microscopical examination (figs. 11, 12, and 13).—The architecture of this tumour was quite different from that of all the others; it was a diffuse growth, limited almost entirely to the grey matter, the thickness of which it had greatly increased. Its blood-vessels had normal walls, and lymphocytes were absent. The number of ganglion cells in the cortex was enormously increased. The cells varied in size from small round to large pyramidal; oval cells predominated, but many cells were pyramidal and polygonal cells were also found. The arrangement of the structures forming the cortex was abnormal; the apical dendrites of the pyramidal cells were not, as is usual, directed toward the surface of the convolutions, but passed indiscriminately in any direction. The

axes of the oval cells lay in all directions. The cortical layers described by Brodmann [2] were disorganized, so that it was impossible to distinguish them; thus where normal cortex merged into neoplasm layers one and five lost their identity, then layers three and six, whereas layers two and four retained their identity longest. The greatest increase in large cells occurred in layers five and six. However, the most remarkable feature was observed in the subpial layer. Normally this does not contain ganglion cells, but in the tumour there were large numbers of small pyramidal and oval cells immediately beneath and in contact with the pia mater, although more primitive cells from which they could differentiate were not present. The surface of the convolutions was irregular and nodular; the nodules consisted of masses of small ganglion cells. Undoubtedly normal ganglion cells were present in the cortex, but in addition there were many other cells which were abnormal in size, shape and distribution. In sections stained with toluidine blue, every cell was seen to have cytoplasm which stained blue and contained Nissl granules; in the larger cells heavier tigroid granules were abundant and were present in the dendrites also. All these cells had an affinity for silver. Implantation cones were absent, yet axis-cylinders arose from many of the cells. All the cells had characteristic large round, vesicular nuclei, each of which contained a deeply staining central nucleolus. The nuclei were not always situated in the centre of the cell; binucleated cells were present in small numbers; more than two nuclei were not observed in any one cell. There was considerable variation in the ratio of the size of the nucleus of a given cell to the amount of its cytoplasm, but in general the nucleus was large in comparison with the size of cell; in the smaller cells, the nucleus occupied most of the cell body. The cells of the tumour had a tendency to grow in groups or clusters. Many, especially in layer six, showed satellitosis. Throughout the tumour astrocytes were increased in number, but all were of adult type; spongioblasts were absent. At the edge of the growth swollen degenerating astrocytes were found; some of these had two nuclei, and therefore had become "gemästete" cells. In spite of invasion and compression of the grey matter, the axis-cylinders in the underlying white matter did not show any signs of degeneration, such as swelling, beading or fragmentation.

This tumour was classified as a gangliocytoma.

The history in Case 8 was of a progressive lesion in the cervical part of the spinal cord for three years. An intramedullary gangliocytoma was partially removed, with temporary improvement. Death occurred seven months later.

Case 8.—A woman, aged 34, came to the Clinic on May 23, 1921, complaining of pain in the shoulders and loss of function of the arms and legs. Three years previously, when three months pregnant, she began to suffer pain in both shoulders; this came in attacks lasting from two to seven days and recurred several times during a month. After this she had no further

discomfort until after delivery, when the pain reappeared and grew more severe. One year previously the pain began to radiate down the inner side of the left arm to the hand, and to be associated with numbness and tingling of the fingers. A year and a half previously she first observed clumsiness and weakness of the left hand; sixteen months later weakness and numbness first of the left leg and then of the right arm appeared, and after a short interval the right leg became weak. During the three months preceding examination she had repeatedly burned both hands without feeling pain.

The patient held her neck stiffly. In both arms, especially in the left, muscular weakness and atrophy were present, particularly in the small muscles of the hands. Power was diminished in the left leg and tonus increased. Sensibility to touch, pain and temperature was moderately impaired over the upper part of the thorax and more so on the inner aspect of the right forearm. Along the inner aspect of the left forearm sensibility to pain and temperature was markedly impaired, but sensibility to touch was practically normal. Sense of position was much diminished in the toes of the left foot, but normal in the right. Vibrations were not appreciated in either leg. The tendon reflexes were not obtainable in the arms; those of the right leg were normal those of the left leg exaggerated. Babinski's sign was present on both sides. There was a little lack of control of both rectal and vesical sphincters. Cerebrospinal fluid obtained by lumbar puncture was clear and colourless; it contained an excess of protein, and six lymphocytes in each cubic millimetre.

On June 9, 1921, the spines and laminæ from the fifth cervical to the second thoracic vertebræ were removed. The spinal cord was greatly enlarged, its greatest diameter being opposite the seventh cervical vertebra; above and below this point the swelling tapered in a fusiform manner. An incision was made in the right posterior column; at once a soft purplish tumour partly extruded. About four-fifths of the tumour was removed, after which the cord collapsed. Convalescence was uneventful. After returning home, the patient gradually improved during July; however, in the beginning of August she began to fail, and died on January 6, 1922.

Microscopical examination.—The tumour was not very cellular. Its blood-vessels were well formed and their walls were for the most part normal, but in one area excessive hyaline thickening of the tunica media was present, of such a degree as almost to occlude the lumen. However, necrotic areas were not discoverable in this part of the growth. Connective tissue and fibroblasts on the one hand, and astrocytes and spongioblasts on the other, were entirely absent.

Although for the most part diffuse, in certain areas the cells of the tumour had a tendency to collect in groups of from three to twenty. The cells were remarkably uniform in appearance; they were relatively large and usually polygonal in shape, seldom pyramidal or round. Their outline was convex, not concave like that of the normal ganglion cells of the spinal cord. Their margins were not always sharp, but frequently faded into the surrounding tissue; dendrites were not numerous, although most cells had one or two

which were small and indistinct. Fine granular Nissl substance was present in the bodies of the cells and in their dendrites; large granules similar to those found in normal ganglion cells were not seen, nor was pigment, so common in the adult ganglion cells of the anterior horns of the spinal cord, found in any tumour cell. The cells had characteristic nuclei, large, round and vesicular, containing one deeply-staining central nucleolus. Binucleated cells were common, but more than two nuclei were rare and giant cells were not found. No immature forms of ganglion cells could be identified. The cells of the growth had a characteristic affinity for silver.

. This tumour was classified as a gangliocytoma.

In Case 9 the history was of a progressive lesion of the cervical part of the spinal cord for four and a half years. Spinal subarachnoid block was demonstrated. An intramedullary gangliocytoma was removed and Roentgen treatment was given. Marked improvement followed.

Case 9.—A woman, aged 27, came to the Clinic on February 5, 1930, complaining of pain in the arms and in the right side of the face and head, and of loss of strength. Four and a half years previously, a few months after the birth of her first child, she began to experience sharp aching pains in the left scapular region. Turning the head increased the pain and caused it to radiate to the left of the neck; however, it was not increased by coughing or sneezing and did not waken the patient at night. Two years previously the pain had spread down the left arm to the hand, especially to the fourth and fifth fingers. One year previously pain appeared in the right side of the face and head: it was sharp and smarting and was associated with flushing of the face; after six months it extended to the right side of the neck and upper part of the thorax. Eighteen months previously the patient noticed loss of power in the left arm, and six months later in the right arm. Three months previously increasing weakness of the legs appeared.

The patient was emaciated. There was moderate flaccid paralysis of both trapezius muscles and of both arms, particularly of the left. Moderate loss of power was noted in both legs. The tendon reflexes were absent in the arms; in the legs they were exaggerated and Babinski's sign was present on both sides; the abdominal reflexes were absent. There was loss of perception of pain and temperature over both arms, and over a band-like zone extending from the second to the fifth rib; above the level of the second rib partial analgesia and thermanæsthesia was determined, including the territory of both trigeminal nerves. Over the lower two-thirds of the trunk, the legs and the anterior aspect of the thighs, partial loss of sensibility to pain and temperature existed; this diminished in intensity from above downward. Sensation was intact over the perineum, buttocks and posterior aspects of the thighs. Vibration was not perceived over the distal ends of the bones of the forearm, and over the right malleoli; over the left malleoli its perception was diminished. Sense of position was lost in the third, fourth, and fifth fingers of both hands,

and somewhat disturbed in the toes of both feet. Cerebrospinal fluid obtained by lumbar puncture was clear and yellowish; its pressure was not altered by compression of the jugular veins. It contained 6 small lymphocytes in each cubic millimetre, and 340 mgm. of protein per 100 c.c. A diagnosis was made of intramedullary tumour.

At operation, the spines and laminae of the second to sixth cervical vertebrae were removed. The theca did not pulsate. The spinal cord was greatly swollen and soft. When the left posterior column was incised an encapsulated maroon-coloured tumour was exposed; the greater part of this was easily separated from the tissue of the cord and removed. Caudally the growth extended to the eighth cervical segment, where a small piece of tumour which was invading the cord was not disturbed. Cranially the growth reached the first cervical segment. Convalescence was at first stormy, probably on account of oedema of the medulla. However, the patient was able to use her legs and her right arm. Following a transfusion of blood on the third post-operative day she improved rapidly, and was dismissed from our care sixteen days after operation. She has returned at intervals for roentgenotherapy, and has regained her physical well-being. At the present time, two years after operation, there is not any evidence of recurrence of the growth. Some weakness persists in the muscles of the shoulder-girdles and hands, and slight weakness in both legs. However, the tendon reflexes of the arm are present. Babinski's sign is still present on both sides. The return of sensation has been less complete: there is almost complete loss of perception of pain and temperature over both arms, over the thorax above the second rib, and over the territory of the upper cervical nerves. Below the second rib there is decreasing analgesia and thermæsthesia down to the level of Poupart's ligaments, below which sensation is normal. Sense of position is completely lost in the fingers, but normal in the toes. Vibratory sense is markedly disturbed over the distal ends of the bones of the forearms, and moderately diminished over the malleoli. The gait is slightly spastic. Control of the sphincters is normal.

Microscopical examination (fig. 14).—This tumour was more cellular than that removed in Case 8. The stroma was scanty, stained pale pink with eosin and did not contain any lymphocytes; neither glial cells nor glial nuclei were present. The blood-vessels were well formed. The cells had a tendency to grow in groups; they varied greatly in size and shape, but most were polygonal. Their cytoplasm was scanty and vacuolated, and contained numerous fine Nissl granules which tended to collect in larger masses at the periphery. The cells had a strong affinity for silver. When present, dendrites were relatively short; they contained Nissl granules. Immature and indistinct axis cylinders were present, but poorly impregnated. The nuclei of the cells were characteristically large and vesicular, and each contained one deeply staining central nucleolus. The size of the nuclei relative to the bodies of the cells was much greater than in normal cells. Usually the nucleus was central; binucleated cells were rare, and more than two nuclei were not seen in any one cell. Only a very few bipolar and unipolar neuroblasts were identified.

The tumour was classified as a gangliocytoma.

COMMENT.

It would be unprofitable to enter into a lengthy criticism of the merits of the various terms which have been applied to tumours containing ganglion cells or neuroblasts; it is undoubtedly true that each author has a good reason or reasons for the term that he uses, and for the most part it is applicable to the tumour he is describing. In our series there are marked variations in the type and in the distribution of the neoplastic cells, and also in the type of supporting structures, so that a descriptive term applicable to one tumour would be unsuited to the others. Our suggestion that the term "neuroblastoma" be applied to tumours containing neuroblasts or primitive nerve-cells, and the term "gangliocytoma" to tumours containing adult nerve-cells, is an attempt to bring the nomenclature of this group of neoplasms into line with that of the gliomas. In one of our cases hyaline connective tissue formed the stroma and made up more than one half of the neoplasm; in another more astrocytes were present than normally; in another some fibroblasts were present, and in still another no stroma of any kind could be demonstrated. Because of these variations in the type of stroma, we have found it impracticable to apply a term which would describe the stroma of each neoplasm as well as the degree of differentiation of the tumour cells themselves, just as pathologists have found it necessary to omit the connective tissue stroma from the names of carcinomas of various organs. As in the gliomas, there was considerable variation in the types of cell which were present in our series of tumours. There was a greater tendency for the cells found in a given tumour to be more uniform in their stage of differentiation than is usually the case in a glioma, although we have described several tumours in each of which several stages of differentiation were present.

The most interesting feature of Case 1 is the fact that the tumour recurred after an interval of six years, and that although both tumours were neurogenic in type, the first was cellular, the majority of the cells being neuroblasts with little cytoplasm and without dendrites or axis cylinders; whereas the second tumour was comparatively acellular, such cells as were present being well differentiated ganglion cells with well-formed dendrites, abundant cytoplasm and Nissl granules. In spite of this difference in the cellularity of the neoplasms, and in the degree of differentiation of the cells themselves, both types of cells had an affinity for silver, and in both nuclei of the same type were present. These were characteristic not only of these two tumours, but of the entire group; they were large, round and vesicular, and contained little

chromatin except one prominent central deeply-staining nucleolus. In the study of neoplasia in general, it is unusual to find that a tumour made up of primitive cells, which has been partially or even almost completely extirpated, should recur after a period of years as a more completely differentiated growth; usually the cells of a recurring tumour are more primitive than those of the original growth. In the more active neoplasm the sparse stroma was younger but less abundant than that of the more highly differentiated tumour, whose stroma contained much hyalinized connective tissue. The structure of their blood-vessels corresponded to the rapidity of growth of each tumour. Both these tumours were infiltrative, thus simulating the macroscopic appearance of most of the gliomas.

In Case 2 the majority of the cells were well differentiated ganglion cells of pyramidal or polygonal shape, but in addition there were some more immature neuroblasts belonging to the unipolar and bipolar stages of differentiation. In spite of the presence of the latter cells the tumour was classified as a gangliocytoma, because mature ganglion cells were dominant. Some of these cells showed slight vacuolization of the cytoplasm, but this had not progressed to the stage of cyst formation so common in gangliocytomas of the sympathetic nervous system. As in our first case the cells had an affinity for silver. Their nuclei were characteristic, and showed deeply staining central nucleoli, as did the nuclei of the neuroblasts also. As in the majority of gangliocytomas, the cells of this tumour had a tendency to grow in groups or small clusters rather than diffusely.

The tumour in Case 3 was classified as a gangliocytoma, in spite of the fact that neuroblasts were present and that mitotic figures were seen. The majority of the cells were well differentiated ganglion cells, which co-existed in some areas with more primitive cells. At least parts of this tumour were growing rapidly, a feature reflected by endothelial proliferation in thin-walled blood-vessels and by areas of necrosis. These necrotic areas explain the presence of the large cysts so commonly seen in gangliocytomas of the brain, and also of the polymorphonuclear leucocytes which were present only in necrotic tissue. Lymphocytes were present everywhere in this tumour; in places they were collected into islands, a common picture in cerebral gangliocytomas. There was little stroma other than the blood-vessels, but near and around the edge of the growth adult astrocytes and some degenerating forms were seen; these did not seem to be growing with the ganglion cells or neuroblasts. In the same areas of the tumour

axis-cylinders derived from invaded brain tissue were present, but it was impossible to demonstrate axis-cylinders arising from the cells of the growth.

Few comments are necessary on Case 4 of this series, as it has been described at length elsewhere[5]. It was classified as a gangliocytoma containing large numbers of neuroblasts; the better differentiated cells predominated only slightly. The situation of this tumour and the associated clinical symptoms were most interesting. In spite of the fact that the patient suffered from evident hypopituitarism, the hypophysis was only slightly compressed, and neither it nor the infundibulum was invaded by the tumour.

In Case 5 the cells of the tumour were quite different from those in any of the first four cases. They were remarkably uniform throughout and simulated astroblasts by possessing abundant homogenous eosin-staining cytoplasm, but there the resemblance ended. These cells had no vascular processes or any affinity for the gold of Cajal's gold chloride and sublimate method. They did have an affinity for silver, and Nissl granules were present, although small and immature and collected especially at the periphery. No well-differentiated adult ganglion cells with dendrites or axis-cylinders were present. The nuclei and nucleoli were characteristic. Stroma was sparse; astroblasts, astrocytes, and spongioblasts were absent, and there was little connective tissue in the neoplasm except around the blood-vessels; lymphocytes were not present. In short, the most interesting features of this tumour were the uniformity of the cells and the complete absence of primitive neuroblasts and mitotic figures.

In Case 6 the tumour cells closely simulated those of Case 5; other points of resemblance were the absence of stroma, the structure of the blood-vessels, the slight amount of connective tissue and the absence of lymphocytes. Primitive tumour cells and necrotic areas were absent. Some of the tumour cells showed numerous small vacuoles at the periphery; in others, these vacuoles were much larger and had led to destruction of the cell body. In certain areas few tumour cells could be seen, but numerous small cysts were present. It was possible to trace all the stages in this process, from vacuoles in the cells to complete destruction of cells and cyst formation. This appearance is rare in gangliocytomas of the brain, but in our experience it is common in similar tumours arising from the sympathetic nervous system. In our series, vacuoles were seen in the cells of certain growths (Cases 1, 2 and 9), but these had not progressed to degeneration and formation of cysts.

It must be emphasized that these cysts are quite different from the larger cysts which are probably the result of necrosis in areas of a tumour.

The tumour in Case 7 was different from all the others of this series, and closely resembles a growth described by Lhermitte and Duclos [7] arising from the cortex of the cerebellum. This was a diffuse tumour; it had produced marked thickening of the molecular layer of the cerebellar cortex, which was almost completely replaced by polygonal and pyramidal types of ganglion cells. In our case the tumour was in the cortex of the right parietal lobe, where the convolutions were flattened, and after excision were seen to be diffusely thickened. Histological study showed the cortex to be composed chiefly of pyramidal cells, but in addition oval and polygonal cells were present. The pyramidal cells did not have their apical dendrone directed toward the surface of the convolution, and the long axes of the other cells lay in every direction. Some very large pyramidal and polygonal cells were present; they contained well-formed Nissl granules, whereas the smaller cells contained finer granules, and the smallest were devoid of demonstrable chromatin substance except that seen in the typical nuclei and nucleoli. All these cells had an affinity for silver which outlined their bodies and dendrites. It was possible to see axis-cylinders arising from some cells, but implantation cones could not be found. Pigment such as is sometimes seen in normal cortical cells was present in only a few cells, which were probably inclusions or remnants of the normal cortex. Where the tumour merged into the normal cortex the Brodmann layers were irregularly involved, and in the tumour itself it was impossible to distinguish the various layers. The superficial layer (layer one or the molecular layer) in which, normally, cells are not present, contained large numbers of very small pyramidal and oval cells lying in contact with the pia mater. In some of the large pyramidal and polygonal cells neurofibrillæ were present, and occasionally these were clumped together as they are in cases of senile dementia.

In Case 8 the neoplasm was in the substance of the spinal cord; it has been described briefly elsewhere [6]. The cells of the growth were large and polygonal. They contained Nissl substance in granules finer than those found in the normal cells of the anterior horns of the spinal cord, and they did not contain any of the pigment which is so common in these cells. Dendrites were almost always present, although they were rudimentary. Axis-cylinders could not be identified arising from any of the cells of the tumour; any axis-cylinders present were probably

inclusions of the invaded tissues of the spinal cord. The grouping of the cells, and their nuclei and nucleoli, were quite characteristic of gangliocytoma.

In Case 9, the tumour was similar to that removed in Case 8. This growth was almost completely encapsulated and enucleable, except at its upper and lower poles; this is not a usual experience at operation in cases of primary tumour of the spinal cord. The cells resembled those in the previous case, except that they showed a tendency to vary in shape; however, polygonal cells were dominant. Nissl granules were larger, especially at the periphery of the cells. The nuclei and the grouping of the cells were characteristic. With the silver impregnation method dendrites and cell bodies were well outlined, and axis cylinders arising from some cells were demonstrated; however, they were immature and stained relatively poorly. No well-formed axis-cylinders, such as might be included from invasion of the spinal cord, were present. This was probably the result of the encapsulation of the tumour; in the presence of such a growth the normal axis-cylinders would be pushed aside, and this is a possible explanation of the marked return of function after operation in this case. The stroma of the growth did not contain any adult or primitive glial cells, or glial fibrillæ. Lymphocytes and areas of necrosis were absent. In one area numerous neuroblasts of bipolar type were found, but the majority of the cells were almost completely differentiated ganglion cells. Therefore, the tumour was classified as a gangliocytoma.

The histological pictures presented by these nine tumours have several points of resemblance. In the majority marked uniformity of cell type was present, with the exception of the tumour in Case 4, in which several varieties of neuroblasts, as well as ganglion cells, were present. Throughout the entire group the nuclei of the neuroblasts, as well as those of the ganglion cells, were characteristic; they were large and vesicular, and each contained a deeply staining central nucleolus. All the tumour cells had an affinity for silver. It was unusual to observe axis-cylinders arising from any of the cells of a growth, and only in the more highly differentiated cells did neurofibrillæ traverse a cell. The majority of the ganglion cells were polygonal, although in one tumour pyramidal cells predominated; however, this was a tumour of the cerebral cortex. The neuroblasts varied greatly in size and shape, and few contained demonstrable Nissl granules; on the other hand practically all the better differentiated cells had definite Nissl substance.

There was a tendency for the adult ganglion cells to grow in groups,

but this arrangement was not so marked as that found in gangliocytomas arising from the sympathetic nervous system. In three tumours of this group (Cases 1, 2 and 9) some cells showed vacuolization of the cytoplasm, and in one tumour (Case 6) this had proceeded to destruction of the cell and formation of cysts; again, this is a more constant finding in gangliocytomas of the sympathetic nervous system. The amount of stroma varied; in several tumours stroma could not be demonstrated. The most interesting difference between any two tumours in this series occurred in Case 1; the original tumour was a neuroblastoma, made up of quite primitive cells, and after partial removal it recurred six years later as a well differentiated gangliocytoma with a stroma of heavy hyaline connective tissue.

There was nothing unusual in the situation of any of these nine tumours, except that in Case 6, which was attached to the dura mater, and not to the brain; grossly it simulated a parasagittal meningioma. There are three possible explanations for this unusual feature; first, that there was a small pedicle joining the brain, which was overlooked at operation, or second that there had been such a pedicle which had disappeared so that the tumour derived its blood supply solely from the meninges; neither of these two explanations is satisfactory. The third and most plausible explanation is that the neoplasm arose from a small heterotopic mass of cortical tissue lying free in the subarachnoid space anterior to the frontal lobes. Heterotopic masses of glial and other cerebral tissues are more common than is generally supposed; frequently we have observed them in the subarachnoid space. However, it has been our experience that such masses are more common around the base of the brain, especially in the posterior fossa, and around the spinal cord, than on the lateral or superior surfaces of the cerebrum. In a study of primary tumours of the spinal cord, Kernohan, Woltman, and Adson [6] encountered three gliomas which did not have any attachment to the cord itself; they felt that these tumours probably arose from heterotopic masses. So far as we can ascertain, this is the only gangliocytoma of the central nervous system which did not have its origin in the substance of the brain or spinal cord. Until further observations are made on other similar tumours, some doubt will remain regarding the real site of origin of this specimen.

This report was limited to a group of cases in which difficulty in the differential diagnosis of glioma, and neuroblastoma or gangliocytoma, did not arise. However, we have encountered several tumours in which both neuroblasts and spongioblasts have been growing side by side;

these have been omitted. Undoubtedly, some authorities will not agree that both types of tumour cells can and do grow together. It is now a recognized fact that medulloblasts are bipotential cells, and frequently we have observed neuroblasts and spongioblasts in medulloblastomas; Bailey and Cushing [1] have reported similar observations. In one case that we have studied, the patient had three separate neoplasms in the left cerebral hemisphere. That in the occipital pole was a spongioblastoma multiforme; that in the parietal lobe was also a spongioblastoma multiforme, but in addition contained many characteristic neuroblasts. In the tip of the left frontal lobe was a third small tumour about 1.5 cm. in diameter, and immediately behind this was a large, smooth-walled cyst about 5 cm. in diameter. The small tumour contained numerous well-formed polygonal ganglion cells growing in small groups, with characteristic cytoplasm, dendrites, nuclei and nucleoli; in addition to the ganglion cells many adult astrocytes of the fibrous type were present, with numerous neuroglial fibrillæ. This case has not been included in the present series because of the complications introduced by the presence of the other growths: it will be reported in a future paper.

Ecology.—The number of cases in the present series is too small to provide any but the broadest outline of the life history of growths of this nature. The cerebral growths may be considered first.

The interval between the onset of symptoms and the establishment of a diagnosis varied widely: thus in Case 1, in which the tumour occupied a temporal lobe, it was five weeks, whereas in Case 4, in which the tumour occupied the third ventricle, it was two years. These intervals are the opposite of those which might have been predicted, for tumours of a temporal lobe are often slow in declaring their presence, whereas tumours of the third ventricle as a rule rapidly give rise to symptoms of increase in intracranial pressure. In Case 4, however, the growth had not obstructed the flow of cerebrospinal fluid. It is somewhat paradoxical that of all the patients in our series the one with the shortest pre-operative history (Case 1) lived longest after surgical intervention. In Cases 2 and 3 the patients died soon after arrival; in neither case would operation have been of benefit. In Case 6 the extra-cerebral situation of the tumour lent itself to radical operation; this patient was alive two years after craniotomy, but it was at least possible that the growth had recurred. Study of the specimens obtained at operation or at necropsy showed very clearly that these growths are rarely sufficiently well demarcated from the surrounding cerebral tissue

to give the surgeon confidence to attempt their radical removal. Only in two instances (Case 1, 1925 tumour, and Case 6) was the tumour encapsulated, and in Case 6 this property may well have been an accident incidental to the extra-cerebral origin of the growth. It is significant that the tumour (Case 7) which was microscopically most highly differentiated, and for this reason most suitable for radical surgical attack, passed imperceptibly into normal brain. It must be concluded, however reluctantly, that tumours of this nature are rarely suitable for operations other than palliative.

The two growths which occurred in the spinal cord also differed one from the other in their enucleability. That found in Case 8 was not encapsulated. It is conceivable, however, that a diagnosis might have been reached a year or more earlier, when a more radical operation might have been possible. On the other hand the growth encountered in Case 9 was encapsulated throughout most of its extent, and therefore was largely removable; however, its upper and lower poles invaded the tissue of the cord, and consequently were irremovable. In this case it is possible that the period of survival and the amount of function retained may be partly accounted for by the persevering use of roentgenotherapy to retard the growth of the portions of tumour remaining in the cord.

SUMMARY.

Nine cases are presented of tumours occupying the central nervous system which were derived from primitive nerve cells. The microscopical appearance of each tumour is described. Tumours of this nature are rarely suitable for radical operation.

PLATE LEGENDS.

FIG. 1 (*Case 1*).—Cellular neuroblastoma removed in 1925. The cell bodies are not clearly outlined, but the round vesicular nuclei and deeply staining central nucleoli are well shown. The cells do not possess definite dendrites. Toluidine blue. $\times 500$.

FIG. 2 (*Case 1*).—Gangliocytoma removed in 1931. The outlines of the nuclei are indistinct, but the nucleoli are sharply stained. Nissl substance can be seen collected at the periphery of the cells. In the cytoplasm of one cell a vacuole is present. Toluidine blue. $\times 1100$.

FIG. 3 (*Case 3*).—The cells tend to grow in small groups, in an cedematous stroma. Variation in the shape of the cells is evident, and the characteristic nuclei and nucleoli are well shown; binucleated and multinucleated cells are present. Toluidine blue. $\times 500$.

FIG. 4 (*Case 3*).—The cells of the tumour contain characteristic nuclei and nucleoli; one cell is multinucleated. Fine Nissl granules are scattered diffusely throughout the cytoplasm of the cells. Toluidine blue. $\times 1100$.

FIG. 5 (Case 4).—Part of a coronal section through the brain, to show the tumour occupying the lower half of the third ventricle; many cysts are apparent in its substance. Its line of demarcation is moderately distinct; the thalami are scarcely invaded by the growth, which has displaced them laterally. Weigert's stain for myelin sheaths. $\times 15$.

FIG. 6 (Case 5).—Anterior views of coronal sections through the brain, to show the tumour occupying the inferior part of the anterior horn of the left lateral ventricle. It has occluded the left foramen of Monro, and invaded the septum pellucidum and the head of the left caudate nucleus. In the photograph on the right the small tumour on the lateral wall of the right lateral ventricle is visible. Reduced.

FIG. 7 (Case 5).—Gangliocytoma in the third ventricle. The cells have indistinct outlines, and multinucleated types are present. The nuclei and nucleoli are characteristic. The cells possess dendrites; in these, and in the cytoplasm, Nissl granules are present. Toluidine blue. $\times 475$.

FIG. 8 (Case 5).—Astroblastoma on the lateral wall of the right lateral ventricle. The cells have abundant homogeneous cytoplasm and delicate processes. The nuclei contain many chromatin granules; a few cells contain two nuclei. Haematoxylin and eosin. $\times 500$.

FIG. 9 (Case 6).—The cells contain characteristic nuclei and nucleoli, and in some fine Nissl granules are present. Stroma is absent. Toluidine blue. $\times 500$.

FIG. 10 (Case 6).—An area of tumour selected to show the formation of cysts. These begin as small vacuoles in the cells. Toluidine blue. $\times 375$.

FIG. 11 (Case 7).—There is considerable variation in the shape of the cells, but pyramidal forms predominate. Binucleated cells are present. Axis cylinders are arising from some cells, and in some cells neurofibrillae are present. Orlandi's silver-impregnation method. $\times 375$.

FIG. 12 (Case 7).—An area of the tumour selected to show the excess of ganglion cells in layer one of the cortex (the marginal glial zone), as well as in layers two and three. The irregularity in the size of the cells and in the direction of their axones is marked. Orlandi's silver-impregnation method. $\times 325$.

FIG. 13 (Case 7).—An area of the tumour selected to show the cells growing in groups in layers five and six of the cortex. Each island gives a false impression of being one multinucleated cell. Satellitosis is present around certain included cortical cells. Toluidine blue. $\times 500$.

FIG. 14 (Case 9).—The cells tend to grow in small groups; they have characteristic nuclei and nucleoli. The stroma is oedematous. Toluidine blue. $\times 500$.

BIBLIOGRAPHY.

- [1] BAILEY, PERCIVAL, and CUSHING, HARVEY. "A Classification of the Tumours of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis." Philadelphia, 1926, 175 pp.
- [2] BRODMANN, KOBBIAN. "Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues." Ed. 2, Leipzig, 1925, 324 pp.
- [3] CAIRNS, HUGH, and RUSSELL, DOROTHY S. "Intracranial and Spinal Metastases in Gliomas of the Brain," *Brain*, 1931, **54**, 377-420.
- [4] COUVILLE, C. B. "Ganglioglioma. Tumour of the Central Nervous System: Review of the Literature and Report of Two Cases," *Arch. Neurol. and Psychiatr.*, 1930, **24**, 489-491.
- [5] DOYLE, J. B., and KERNOHAN, J. W. "Ganglioneuroma of the Third Ventricle with Diabetes Insipidus and Hypopituitarism," *Journ. Nerv. and Ment. Dis.*, 1931, **73**, 55-61.
- [6] KERNOHAN, J. W., WOLTMAN, H. W., and ADSON, A. W. "Intramedullary Tumours of the Spinal Cord. A Review of Fifty-one Cases, with an Attempt at Histologic Classification," *Arch. Neurol. and Psychiatr.*, 1931, **25**, 679-699.
- [7] LHERMITTE, J., and DUCLOS. "Sur un ganglioneurome diffus du cortex du cervelet," *Bull. de l'Assn. franc. pour l'étude du cancer*, 1920, **9**, 99-106.

PLATE VIII.

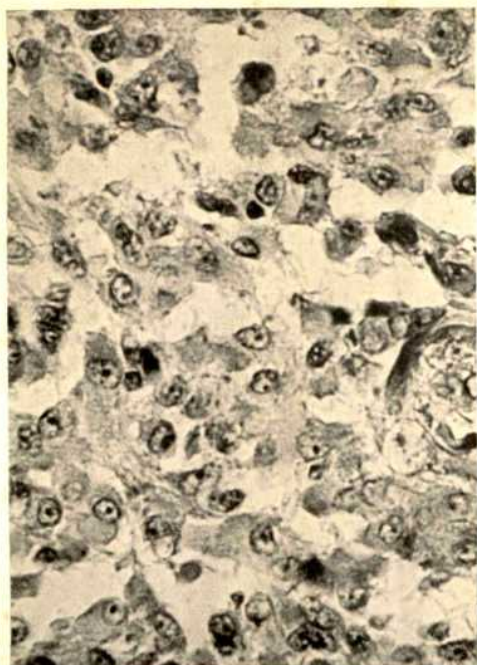


FIG. 1.



FIG. 2.

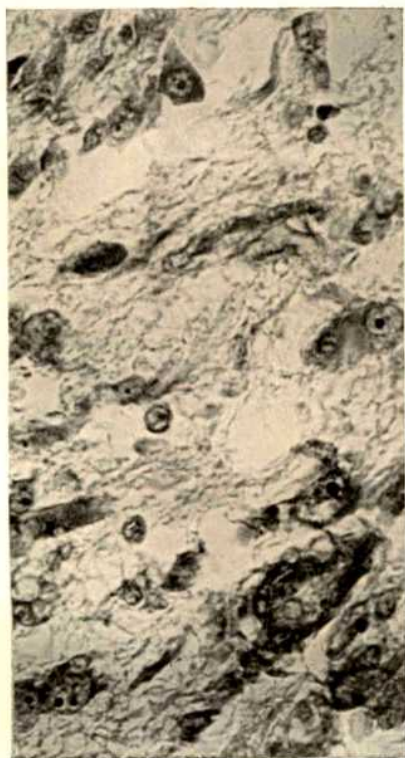


FIG. 3.



FIG. 4.

To illustrate paper by Kernohan, Learmonth and Doyle.

PLATE IX.



FIG. 5.

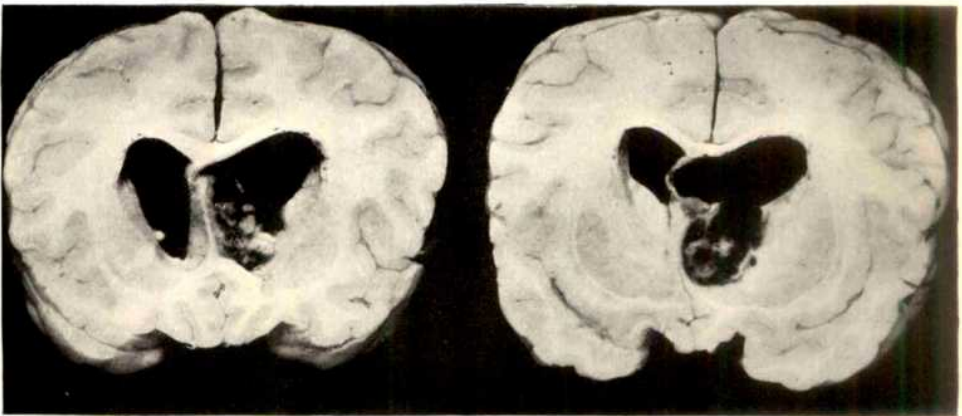


FIG. 6.

To illustrate paper by Kernohan, Learmonth and Doyle.

PLATE XI.



FIG. 11.

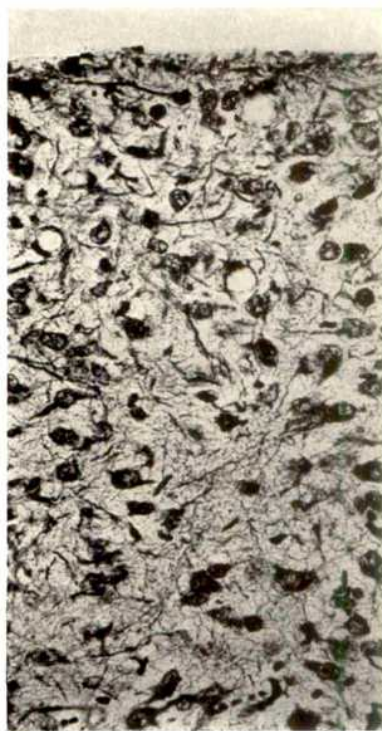


FIG. 12.



FIG. 13.



FIG. 14.

To illustrate paper by Kernohan, Learmonth and Doyle.

PLATE X.



FIG. 7.

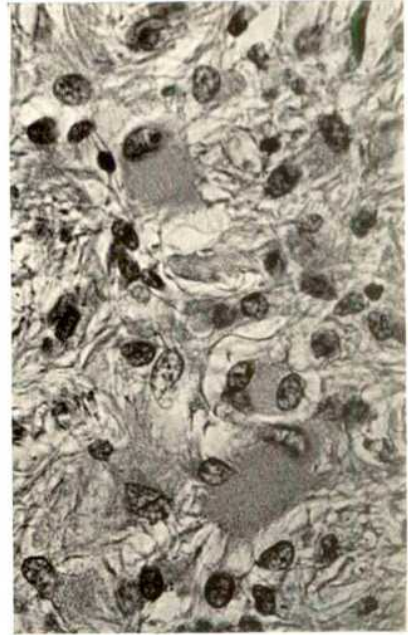


FIG. 8.

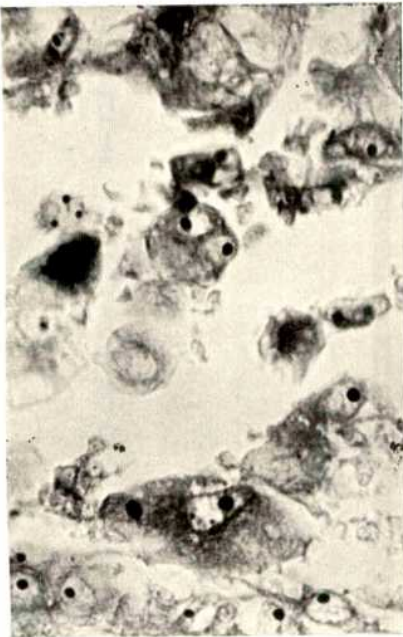


FIG. 9.

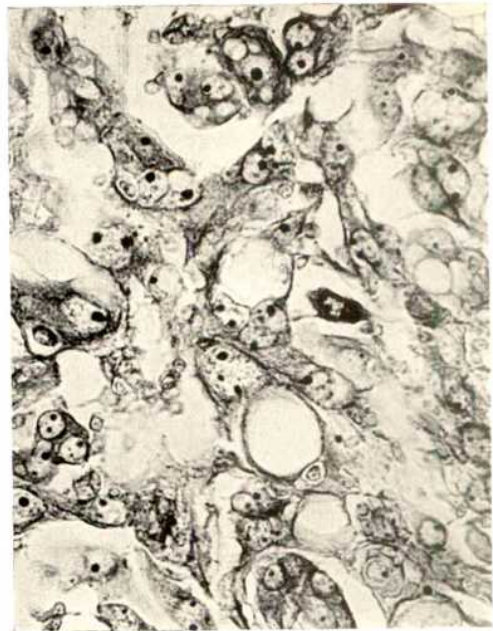


FIG. 10.

To illustrate paper by Kernohan, Learmonth and Doyle.

TUBEROSE SCLEROSIS AND ALLIED CONDITIONS.

BY MACDONALD CRITCHLEY AND C. J. C. EARL.

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CHAPTER I.—HISTORICAL SURVEY.

THE first recognitions of that special form of cerebral sclerosis which we speak of as "tubero-se" or "tuberous" are based upon a few isolated pathological descriptions. Probably the earliest record was a case described by von Recklinghausen [56] in 1863. In the brain of a newly-born child a large number of sclerotic areas were found; there were several myomata growing from the heart muscle. We have been unable to secure the original communication, and further details are not available. Hartdegen [34], early in 1881, described a child of two days, of healthy parentage, who died in convulsions. Autopsy revealed spina bifida, purulent spinal meningitis, areas of sclerosis throughout the cerebral cortex and a number of small tumours projecting into the lateral ventricles. The cerebral lesions were made up of glial hyperplasia, containing a number of ganglion-like cells of exceptional size, the processes of which, together with those of the glia cells, formed a close network. Hartdegen applied the term "glioma gangliocellulare cerebri congenitum" to this case.

We are indebted to the Medical Research Council for the defrayment of the expenses of this paper.

Bourneville [13] was perhaps the first to recognize the condition as a pathological entity. In a series of publications between 1880 and 1898 [13-22], he drew attention to a rare form of multiple cerebral sclerosis occurring in young patients who had shown during life mental deficiency and epilepsy. This condition he called "tuberosc sclerosis" from the potato-like appearance of the morbid foci. His accounts were mainly pathological and he did not consider it possible to diagnose tuberosc sclerosis during life. He was inclined to attribute the disorder to the results of a meningitis or a meningo-encephalitis.

Bourneville noted a frequent co-existence of tumours of the kidney of a primitive "mixed" histological character.

More detailed histological studies of the brain were made in the following years, notably by Geitlin, Brückner, Pellizzi [52], Perusini [53], de Montet [48], Campbell [26], and Vogt [63]. In recent years, outstanding pathological contributions have been made by Bielschowsky and his associates [6, 7, 8, 9, 10], Josephy [41], and von Meduna [67].

Subsequent reports confirmed the association of neoplasms of the kidney with tuberosc sclerosis, and growths were also at times found in the heart, spleen, lungs and retina.

Bourneville noted the co-existence of another anomaly, namely, adenoma sebaceum. This had been described by Balzer (1885-86) [2, 3] and also by Pringle [55], as a hyperplasia of certain elements in the skin, distributed in a curious butterfly fashion upon the face, and associated not infrequently with epilepsy and intellectual subnormality.

Bourneville regarded the occurrence of adenoma sebaceum as coincidental, and for years tuberosc sclerosis was looked upon as a pathological curiosity. Later, however, principally owing to the work of Vogt in 1908, the clinical syndrome of mental deficiency, epilepsy and adenoma sebaceum emerged, and series of such cases were reported by Sherlock (9 cases) [61], Lind [46], and Brushfield and Wyatt (16 cases) [23]. It also became evident that incomplete forms of the syndrome occurred. Schuster, in 1913 [59, 60], described a case of tuberosc sclerosis with adenoma sebaceum occurring in a young man of normal intellect though subject to epilepsy. It was recognized, too, that the cerebral condition might exist in the absence of one or even of all of the classical clinical signs. Recent contributions have dealt largely with its pathogenesis, histology, the clinical aspects of abortive and atypical forms, and with the association of the disorder with von Recklinghausen's disease.

One of the chief difficulties in the description of such a protean disorder involving numerous systems of the body and exhibiting various *formes frustes* is the question of terminology. The term *epiloia*, originally proposed by Sherlock, is applied by psychiatrists to connote the complete syndrome of mental deficiency, epilepsy and adenoma sebaceum. The name has been severely criticized, but it serves a purpose and is now sanctioned by use. For the less complete forms in which any one of the pathological findings may exist alone no suitable name appears. Tuberoze sclerosis is perhaps the most constant feature, and we feel that in the absence of an adequate inclusive title we should adopt tuberoze sclerosis as the most informative, restricting *epiloia* to the severest grades, and designating the abortive monosymptomatic forms by some purely descriptive label, e.g., "renal tumour," "adenoma sebaceum."

CHAPTER II.—THE CLINICAL ASPECT.

Our present series comprises twenty-nine cases, all of which, with the exception of No. 23, were personally studied. Twenty-two were patients at Caterham Mental Hospital; five of them were inmates of the Fountain Mental Hospital, one was a patient of the Manor and one died at Leavesden Mental Hospital. To Drs. Lindsay, J. Nicoll, E. Littlejohn and R. M. Stewart, the respective medical superintendents of these four institutions, we accord our thanks for their kindness in allowing us to examine and record these cases. Four patients in our series died and the central nervous system and the visceral growths were studied in detail.

Ætiology.—Tuberoze sclerosis appears to be commonest in European countries, especially Great Britain, although cases have also been recorded from Australia and the United States, and once from Brazil. Almost all the subjects were of white race, Jews and Gentiles alike being affected, and, as with other types of cerebral degeneration, tuberoze sclerosis is commoner among the "lower classes" of the community.

The family history frequently presents important facts, as evidence of tuberoze sclerosis or various abortive forms of the syndrome amongst the siblings or progenitors, though it is probable that the true nature of the *formes frustes* is frequently not appreciated. The point is well illustrated in Berg's account [4] of a father and daughter who showed adenoma sebaceum, epilepsy and slight mental impairment, with typical post-mortem findings of tuberoze sclerosis and renal tumours. The grandfather had died after a renal operation and at autopsy a

"mixed" tumour of the kidney was found without other features suggestive of tuberose sclerosis.

Schuster's first case, a boy aged 16, showed during life adenoma sebaceum, epilepsy and signs of intracranial tumour. Autopsy revealed tuberose sclerosis and multiple renal tumours. The boy's mother had numerous *café au lait* patches and a black nævus on the left arm; his maternal grandmother had multiple nævi, his mother's grandmother was an epileptic, and convulsions in childhood had occurred in his mother's sister. A paternal cousin of the mother was also epileptic.

In Koenen's family six individuals were affected in three generations. A family recorded by Dobson [28] is an example of grossly degenerate stock on both sides. A girl, aged 10, died at Wakefield Asylum of epilöia. Her brother was epileptic and very unstable; the mother was "nervous," and two maternal uncles had died in convulsions in early childhood. A maternal grand-uncle was alcoholic and died of general paresis; a maternal grand-aunt had "alcoholic pseudo-paresis." A paternal uncle was intemperate.

Often the family history shows no evidence of tuberose sclerosis but bears a strong psychopathic taint. Epilepsy and alcoholism are common and in many cases psychoses have occurred. In de Montet's case manic-depressive psychosis occurred in the ancestry, and a family history of dementia paranoïdes was obtained in the second of the cases reported by Kreyenberg, Delbanco and Haack [43]. A parent died of tabo-paresis in Lázár's case [44].

In our series a family history was obtainable in twenty instances only, marks of psychopathy being present in the following thirteen cases:—

- Case 1.—Both parents alcoholic.
- Case 5.—Grandfather died at 26 with epilepsy.
- Case 6.—Uncle insane.
- Case 7.—Father at present in an asylum suffering from epilepsy, paranoïa, and adenoma sebaceum of the face. A brother is an epilöiac.
- Case 8.—Maternal cousin in an asylum.
- Case 10.—Father alcoholic. Mother and aunt feeble-minded. One sister "dull." Two siblings died in infancy.
- Case 11.—Maternal grandfather epileptic.
- Case 14.—Mother, mother's cousin and mother's uncle have facial adenoma sebaceum.
- Case 16.—Mother's sister in asylum.
- Case 17.—Mother had facial adenoma sebaceum, but no gross mental defect. An uncle and one brother died insane. Father emotional and unstable.

Case 20.—Maternal cousin epileptic.

Case 21.—Mother in an asylum. Patient's elder brother has adenoma sebaceum. Mother's brother "rash on face," and "simple-minded."

Case 24.—Father died in an asylum. Brother died in an asylum with epilepsy.

It has not been possible to investigate the family history of all our cases more fully to determine how many of the psychotic members actually showed evidences of tuberoze sclerosis.

Factors of possible importance are the questions of place in family, the age of the parents at the time of conception, the state of the maternal health during pregnancy and the details of the confinement. In fourteen cases only in our series was it possible to obtain details as to place in family; the facts are as follows:—

Case 1.—Third of seven children.

Case 2.—Fourth of five children.

Case 5.—Second of four children.

Case 8.—Third of four children.

Case 11.—First of two children.

Case 12.—Third of five children.

Case 13.—Third of six children.

Case 19.—Third of three children.

Case 21.—Third of three children.

Case 24.—Third of five children.

These findings contrast with those in Brushfield and Wyatt's series, where eight out of sixteen patients were first-born.

The age of the parents at time of conception has unfortunately been noted only fourteen times in our patients. The average of these gives 33.14 and 30.71 years as the age at time of conception of the father and mother respectively. In ten of Brushfield and Wyatt's cases the age of both parents was over 30 at the time of birth.

Details as to the mother's confinement and labour have not been available in many of our cases nor in cases on record. In one of our series, the notes state that the patient was a six months' premature child (though it weighed 7½ lb.) and that labour was preceded by a fright.

All writers on this subject now agree in exculpating syphilis as a factor in the ætiology of tuberoze sclerosis, although Scarpatetti [68] regarded parental syphilis as the responsible agency.

Symptomatology.—The clinical features are difficult to describe under one head.

In the incomplete forms, which are common amongst the members of the family of an epiloiac, there may be no resultant disability, so that the real nature of the *forme fruste* is usually undiscovered.

In the true epiloiac symptoms and signs appear in infancy or early childhood. It is usually stated that the earlier the onset the more rapid the course. The first case on record is actually also the youngest, for Hartdegen's patient died at the age of 2 days.

Usually the first abnormality is developmental delay such as characterizes mentally defective children in general, the child failing to sit up, crawl or walk until an unusually late age. Talking is usually very late and many lower-grade patients remain mute. Out of thirteen of our patients in whom there was a note on speech development, two commenced to talk at 12 and 13 months respectively, one at 4 years, one at 7, one at 9, whilst 8 failed to develop speech.

The degree of mental defect varies widely from case to case. It is usually obvious by the third year, and in all our cases in which the point can be ascertained mental defect was observed before the sixth year.

Cutaneous lesions make their appearance usually within the first decade, and may advance somewhat abruptly at puberty. The skin affection which attracts attention consists in a red papular rash over the nose and cheeks, recognizable as adenoma sebaceum. It is impossible to say at what age the other dermatological lesions appear on the trunk and extremities, and it is a matter of experience that these may be overlooked by the parents, until attention is directed to them in the course of medical examination.

At about the time of the second dentition the patient may begin to lose ground and show increasing dullness, disordered conduct, spitefulness, emotional outbursts and impairment of speech. In many such instances admission to an institution became necessary. The course of the epiloia is rapidly downhill after puberty; death usually takes place in the second decade from cachexia, pulmonary disease or status epilepticus. One of our patients, however (Case 14), dropped dead quite suddenly while at play. In this case gross cardiac disease was found at autopsy. In Lind's series the oldest patient died at 47, the youngest at 4; in our four fatal cases, death occurred at 14 in one instance, and at 17 in the other three.

In the incomplete variants of this disorder, the clinical course may differ considerably. Thus, in those cases where adenoma sebaceum is in the foreground, neuro-psychiatric features may be inconspicuous and not progressive. No shortening occurs in the expectation of life

and the patient may remain a useful working member of the community.

A still rarer development and mode of termination is exemplified by those cases which show in early adult life signs of raised intracranial tension, at times accompanied by focal neurological signs (Schuster, Kaufmann and Fischer, Bychowski [25]). We have been privileged to examine the brain of a case of this type. A girl, aged 8, was admitted to the Richmond Hospital, Dublin, under the care of Mr. McConnell, on account of headache, vomiting and defective vision. Petit mal attacks had been present for many years, but there was no gross mental defect. Examination revealed bilateral papilloedema but no localizing neurological signs. At post-mortem examination there were found cerebral changes typical of tuberose sclerosis, and in addition a gliomatous tumour the size of a walnut in the posterior portion of the third ventricle.

Lastly, a few patients have succumbed after operations for the removal of a visceral growth the symptoms of which form an important part of the clinical picture.

Epilepsy, which constitutes a frequent and important symptom in both typical and atypical cases, varies widely in its clinical features. In the epilolia group it is especially frequent, being absent only twice from our series of twenty-nine cases, and once also from the Brushfield-Wyatt cases and the series recorded by Bourneville. It usually makes its appearance within the first two years of life.

All types of attack may be encountered, grand mal, petit mal and Jacksonian. Equivalents are not uncommonly present, in the way of giddy attacks, paroxysmal outbursts of passion, "absences" and the like. Two of our patients exhibited varieties of epilepsy procursiva.

The frequency and periodicity of attacks are very variable in individual cases. While some patients have as many as ten or twelve fits daily, others, such as our Case 10, have merely one or two in a year. Attacks of serial epilepsy may occur, though the intervals of freedom may be extremely irregular. One striking feature in many epiloliacs—which distinguishes them from other cases of epilepsy with mental defect—is the very long periods of remission which may be present. Some of our patients, who were previously suffering numerous attacks, would suddenly go for a period of years without a fit. In Case 24—where the patient showed no mental impairment—there was a remission of seven years. These periods of freedom occur irrespective of treatment. During these remissions the mental deterioration usually continues steadily,

thus emphasizing the lack of correspondence between the severity of the epilepsy and of the idiocy. Gallus has stated that the epiloiac never develops the characteristic "epileptic temperament" which might be expected in an individual sustaining a large number of attacks.

As a terminal feature, the epileptic fits may increase considerably in number; thus during the last twenty-four hours of life, our Case 5 had 111, and Case 19, 119 fits.

Neurological manifestations.—The physical appearances of the patient with tuberosc sclerosis are usually striking enough to betray the diagnosis immediately. The presence of the facial eruption at once arrests attention and closer examination usually reveals other abnormalities.

Most of the individuals are noticeably undersized for their years, without however showing any infantilism or absence of secondary sexual features. Stigmata of degeneration are usually demonstrable in the lower-grade patients. In our experience the commonest marks have comprised: (1) the simian hand (flattening of the thenar eminence, with inversion of the thumb and flexion of the terminal phalanx); (2) shortness and incurving of the little finger; (3) ears which are misshapen, asymmetrical, protruding or excessively large. Numerous other stigmata have been encountered, such as hemihypertrophy, epicanthus, high palate, supernumerary digits, hydrocephalus, syndactyly, spina bifida, and cranial anomalies. Lázár mentions adiposo-genital dystrophy in a patient with tuberosc sclerosis. Several patients in our series were highly myopic; a few showed strabismus. It is interesting that enamel defects, irregular arrangement of the teeth, and other dental abnormalities are absent.

Neurological examination is at times entirely negative; more often, however, minor anomalies are demonstrable in the motor system. The low grade of the mental state and the not infrequent resistivity usually precludes satisfactory investigation.

The ocular mechanisms are usually healthy, as instanced by normal pupillary reactions and ocular movements, absence of nystagmus and normal media. Van der Hoeve [36 and 37] has drawn attention to the occurrence of flat tumours or "phakomata" on the retinae of patients suffering from tuberosc sclerosis. Although he judged this finding not uncommon, having seen it in both eyes of every one of his six patients, we have found them once only in our series. More recently, they have also been noticed in cases of tuberosc sclerosis by Feriz and by Nitsch. These "phakomata" appear on ophthalmoscopic examination as oval or circular areas, white or grey in colour, situated in the retina away from

the disc. Their diameter is about half that of the papilla. No close relationship with the blood-vessels exists; there is no surrounding tissue reaction.

Papilloedema does not occur in tuberoze sclerosis, except in those very rare cases of coincident intracranial neoplasm.

More detailed examination of the motor system shows usually no focal muscular atrophy; the crude strength—as far as accurate testing is possible—appears normal in the patients who have no local paralysis. An alteration in muscle tonus is common, however. In the younger individuals definite diminution in tone is usual, allowing of undue mobility at the joints; in older patients this hypotonus is usually replaced by rigidity. As a rule it is impossible to investigate this point more closely, as a certain amount of negativism is generally present. Catatonia is often found, especially in this latter type of patient.

Highly characteristic of the mentally defective patients with tuberoze sclerosis is a peculiar type of motor restlessness which is described later.

Accurate investigation of sensibility is not possible. In such patients as are able to co-operate at all, the special senses and cutaneous sensation appear to be normal. Some of the lower-grade patients are indifferent to any but grossly painful stimuli.

Local paralyses are at times met with in this condition, comprising a monoplegia, hemiplegia, paraplegia, or tetraplegia. A hemiplegia was found once in our series and a diplegia twice. In these two latter cases the diplegia was of the "atonic" variety, with absent tendon reflexes, flaccidity and plano-varus deformity of the feet.

Cerebellar signs occurred once only in our series, and we know of no record of similar finding in the literature.

Case 25.—A female, aged 35, was of such defective mentality as to be unable to furnish any history whatever. No records were available as to the development of her symptoms. She was an epileptic and showed numerous cutaneous anomalies, such as diffuse pigmentation of head and back; a large *café au lait* patch over left axilla and scapular region and another under the left breast; vitiligo over neck; scanty, pale type of facial adenoma sebaceum. She had a constant nodding movement of the head, and the speech was grossly dysarthric and staccato. Nystagmus occurred on lateral deviation of the eyes; hypotonus and a cerebellar type of inco-ordination were demonstrable, associated with an intention tremor. The tendon reflexes were extremely brisk; plantar responses flexor in type. No obvious sensory loss. Optic discs normal. Gait wildly reeling

Owing to the lack of family and personal history, it is impossible to say whether these signs indicate a chance co-existence of tuberoze

sclerosis with an heredo-ataxia, or whether there is a more intimate association.

Speech is usually grossly impaired in well-marked cases.

The reflexes are generally unaltered in the earlier stages, but in older patients with hypertonus there may be some liveliness of the tendon responses. Plantar responses are of the flexor variety, except in the diplegic cases. We have found no abnormality in the abdominal responses.

Psychological.—Tuberose sclerosis is an heredo-familial degeneration, and those afflicted may be expected to show some degree of mental inferiority. The psychological aspect of subjects suffering with the various *formes frustes* has never been studied, but, as our cases show, a strong familial psychopathic taint is common, whilst the great majority of patients with adenoma sebaceum are known to be mentally defective though not necessarily epileptic.

In our series one patient was mentally normal. Three others were defectives without epilepsy; all three were adult females, their mental ages on the Terman Binet scale being 8 years, 5 years 2 months, and 5 years 4 months. Emotionally the first of these was entirely stable, the second facile and excitable, and the third wildly unstable and subject to fleeting persecutory delusions.

The essential feature of the psychology of epilepsy is a combination of intellectual defect proper with a primitive form of psychosis. The intellectual defect is always pronounced, all of our cases falling into the categories of imbecility and idiocy. The psychosis always resembles a primitive type of catatonic schizophrenia, though the exact form of the reaction varies with the level of mental development at which it occurs.

The depth of psychosis is independent of the degree of intellectual defect, although the two processes are so inextricably intertwined as to render impossible any accurate estimation of the part played by either in any given case. In the following account, therefore, the grouping for descriptive purposes into "high" and "low" grades is somewhat arbitrary and is based largely upon the adaptive reactions, with relatively little reference to the potential intelligence.

The high-grade patients are usually relatively intelligent in childhood. Signs of defect appear early and there is delay in walking and talking, but the children are quite trainable in an imbecile school and may even learn to read and write a little. Screaming fits are very common—they occurred in all the cases of which we have obtained reliable records—and the children usually play with their fingers a good deal. Otherwise

they appear temperamentally normal and are sometimes described as cheerful and affectionate. The earliest signs of psychosis occur as a variability—independent alike of fits or of discoverable external cause—in the degree of environmental adaptation achieved. This is first seen at or after the fifth year, occurring as periods of hours or days during which the patient appears vague and preoccupied and is mentally inaccessible. At or before puberty some degree of dissociation is usually permanently installed, though subject to wide and prolonged variations in degree. At this time, too, rapid deterioration may occur, so that patients who have hitherto ranked as high grade must now be relegated to the low-grade group.

Those who remain sufficiently high-grade now show marked personality changes, the states of preoccupation are longer and more frequent and the patients grow solitary, silent and apathetic and liable to sudden brief outbursts of motiveless excitement similar to those seen in catatonic schizophrenics. They usually resent interference and become dangerous to other patients and sometimes to themselves, though the self-injury is always slight and suicidal attempts do not occur. Speech which may have been fairly fluent now falls off, they use very few words and may show echolalia and short perseverative repetition of phrases, or may become almost entirely mute. Three of our cases showed the "secret speech" of dementia præcox.

The degree of catatonia varies. A certain amount of rigidity may be present and *flexibilitas cerea* is common. Several of the patients appear semi-stuporose and one girl has lain in a negativistic stupor for months on end.

The tendency to hand-and-finger-play remains, though it is not so marked as in the low-grade group. The more psychotic patients are usually to be seen sitting apathetic, their hands clasped on their laps with fingers slowly twisting. Two of the least psychotic of the high-grade patients, who commit self-injury when annoyed, do so by violently biting their hands.

The mental content of the psychosis cannot be assessed, as these people have not sufficient intelligence to communicate their thoughts, but it is significant that in three of five patients from whom drawings could be obtained, these showed grossly psychotic trends with idiosyncratic details and crude sexual symbolism. The fourth drawing was of bizarre type and the fifth, which was obtained from the least dissociated of our patients, was the usual imbecile production but showed marked perseveration, the entire page being covered with drawings

and letters in response to the command, "Draw a man"! This patient gave a psychotic response in the "manikin" test. The following case illustrates this particular type of epiloia:—

Case 14.—E. B., female, aged 28. *Family history:* Maternal grandmother and grand-uncle had adenoma sebaceum. On admission at age of 24, showed adenoma sebaceum. She was simple, childish but quarrelsome; speech slow and hesitant. Epileptic fits occurred at monthly intervals. On examination, she lay in a catatonic attitude, smiling to herself. The speech was hushed and barely audible. Simian hands. A gross catatonic tendency existed in arms and legs. Tonus was diminished in the arms and increased in the legs. Tendon-jerks brisk; pupillary responses rather sluggish. Adenoma sebaceum; large sacral plaque of molluscum fibrosum; a few fibromata over the trunk.

The low-grade group shows a similar, though more primitive reaction. Mental development is later and less complete than in the high-grade cases and deterioration commences earlier. Speech development is absent or very poor, and in the developed psychotic stage mutism is constant. Such children are not silent, however, for they make curious animal-like sounds, and by varying intensities can often make known their wants or feelings. The variation in accessibility is not so striking as in the higher-grade patients, though probably always present. Screaming fits and causeless crying are very frequent. Violence and self-injury are less common than in the high-grade group.

All manner of bizarre attitudes and stereotyped movements occur, and these are most striking in the hands and fingers. Somewhat similar hand movements sometimes occur in simple aments of the idiot grade, but they are uncommon and are very rarely complex, whilst in the low-grade epiloiac they are a constant feature, frequently indulged in, and often of an amazingly complicated nature. These movements appear to have some significance for the patients; they occur when the appearance of dissociation is most marked, and the eyes usually fixate the moving hand. Thus one boy has been seen with a rapt expression keeping up a highly complicated rapid movement of his right hand and slow and entirely different movement of the left, completely indifferent to his neighbour who was hitting him vigorously on the head with his open hand. Another boy who has frequent fits of crying holds his hand in a curious attitude in front of his eyes when he is crying. Primitive erotic movements of rocking and swaying are always present and usually frequently indulged in. Less common features observed in this group are head banging of a very violent type, rumination and aerophagy.

Dissociation is frequently profound, the patient appears completely

unconscious of his surroundings and tolerates an extraordinary amount of physical interference. Such patients take no interest in their food except to play with it, and are liable to lose much weight from under-nourishment. Catatonic rigidity is constant and *flexibilitas cerea* frequent, though the relative activity of most of these patients renders the term stupor hardly applicable. Patients in this group cannot be credited with "thought" and it is impossible even to guess at their subjective processes, but from the sudden fixation of their gaze upon nothing and from their air of listening—again to nothing—intently and with a strange and alien smile, it seems possible that they undergo some crude hallucinatory experiences.

This low-grade type of patient is illustrated by the following case report:—

Case 2.—E. A. F. T., male, aged 11. Family history unimportant. Patient is said to have been born three months prematurely though the weight at birth is reported as $7\frac{3}{4}$ lb. He walked and talked at one year; convulsions first appeared at 15 months and have continued at intervals. On admission at the age of 4 years and 3 months, he was a low-grade imbecile, wet and dirty, requiring to be fed. He could not understand sentences but would repeat words. Within the next few years, adenoma sebaceum was noticed on the face. His mental state deteriorated and he showed a fondness for regurgitation and rumination. On examination he was found curled up; he was unable to talk but chattered rapidly and quietly to himself. He resisted examination. No neurological abnormality existed other than slight hypotonus. When excited he showed bizarre hyperkinetic movements of the hands and fingers. No stigmata of degeneration. Marked adenoma sebaceum; a round, flat fibroma on the neck, with several smaller nodules on trunk; one area of pigment over the right scapula and numerous small apigmented patches (see fig. 2).

In the most profound cases there is complete apathy and occasionally even a failure to chew or to swallow. In this group it is impossible to say how much of the final result is to be ascribed to dissociation, and how much to amentia, though it is almost certain that both factors are always present. Any variation in accessibility is most difficult to demonstrate, though there is usually a history of some deterioration and there may be occasional "flashes" of spitefulness. One exceptional case, a helpless idiot, showed an improvement in her 13th year, and now at 16 is classed as a low-grade imbecile able to walk and talk.

It was possible to submit five epiloiaes to psychometric tests. These patients are particularly difficult test subjects on account of their verbal paucity or mutism, and their marked inaccessibility. The test-series adopted was the Merrill Palmer scale for pre-school children, all

verbal tests and all tests involving direct imitation being scored as omissions, thus using the tests as a performance series.



FIG. 1.

FIG. 1.—Showing a number of pedunculated dermal tags on the neck in the case of an epiloia patient.

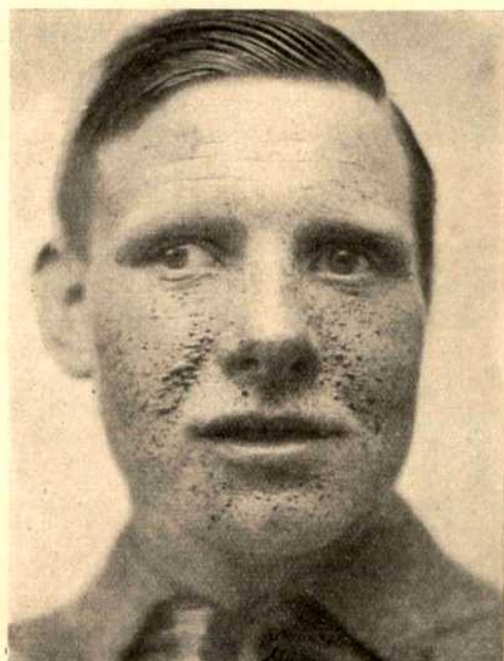


FIG. 2.

FIG. 2.—Well-marked facial adenoma sebaceum in a patient with epiloia.

TABLE I.—PSYCHOMETRIC TEST RESULTS (MERRILL PALMER SCALE).

Case No.	Sex	Age	Mental age	Intelligence quotient	Degree of dissociation
4	M.	19	2 years 3 months	16.0	Severe; almost inaccessible
5	M.	17	5 " 10 "	41.6	Slight
6	M.	19	5 " 11 "	42.25	Semi-stuporose
13	F.	16	3 " 8 "	26.14	Slight
14	F.	28	5 " 3 "	31.5	Semi-stuporose

The results, which are shown in Table I, are presented because of the striking evidence they afford of the potential intelligence of the subjects as compared with their adaptive behaviour. The proper

evaluation of the scores obtained is doubtful, involving, as it does, the application to adolescent and adult defectives of a scoring intended for normal young children. Moreover, the quantitative results of psychometric tests on psychotic subjects must always be accepted with reserve; there is no doubt that in this series the scores obtained were definitely below the subjects' true potentiality.

Qualitatively the tests gave valuable information. The subjects appeared to understand the instructions given to them, and such tests as were accepted were intelligently approached, muscular co-ordination and the handling of concrete material being surprisingly good.

Behaviour under test showed obvious indications of psychosis in all cases. Two patients failed in block building tests because they became dissociated and built designs of their own instead of following instructions, whilst all the patients showed a tendency to dissociation on meeting with difficulties. In one case this caused the only failure, the rest of the performance being well above the imbecile level. One patient lost a great many marks because he insisted on holding all his fingers extended throughout the test, which rendered his performance very slow.

The varying degrees of dissociation were well displayed. Four of the five patients tested were apathetic, and two of these were practically stuporose. These last were most striking, being roused with great difficulty from semi-stupor, performing a test cleanly and showing quite a degree of interest, only to relapse into their former state immediately afterwards. One boy who had kept up an amazing series of attitudinizations and elaborate movements of his hands, suddenly ceased, and filled the Wallin peg boards quickly and neatly, in thirteen and fourteen seconds respectively, to return at once to his movements, whence no further stimulation could arouse him.

Dermatological.—We now realize the great importance and diagnostic significance of cutaneous anomalies in the symptomatology of tuberose sclerosis.

The chief of these skin lesions is, of course, facial adenoma sebaceum. To-day we rely strongly on this physical sign in making the diagnosis, and one would hesitate to diagnose tuberose sclerosis in the absence of adenoma sebaceum, except among those members of a family of tuberose sclerosis who show neurological or psychical abnormalities.

According to Sutton, adenoma sebaceum was first described by Rayer, but priority is usually given to Balzer. Five years after Balzer's first communication Pringle described carefully the clinical and histo-

logical characters of the disease, and suggested the term "adenoma sebaceum." From that time a large number of cases have been recorded by dermatologists, and certain aetiological and clinical peculiarities have been noted. Thus it was found to occur early in childhood or occasionally at birth, usually increasing rapidly at puberty. Only exceptionally did the onset date from early adult life. The heredo-familial tendency and the frequent association of intellectual defect and of epilepsy were noted.

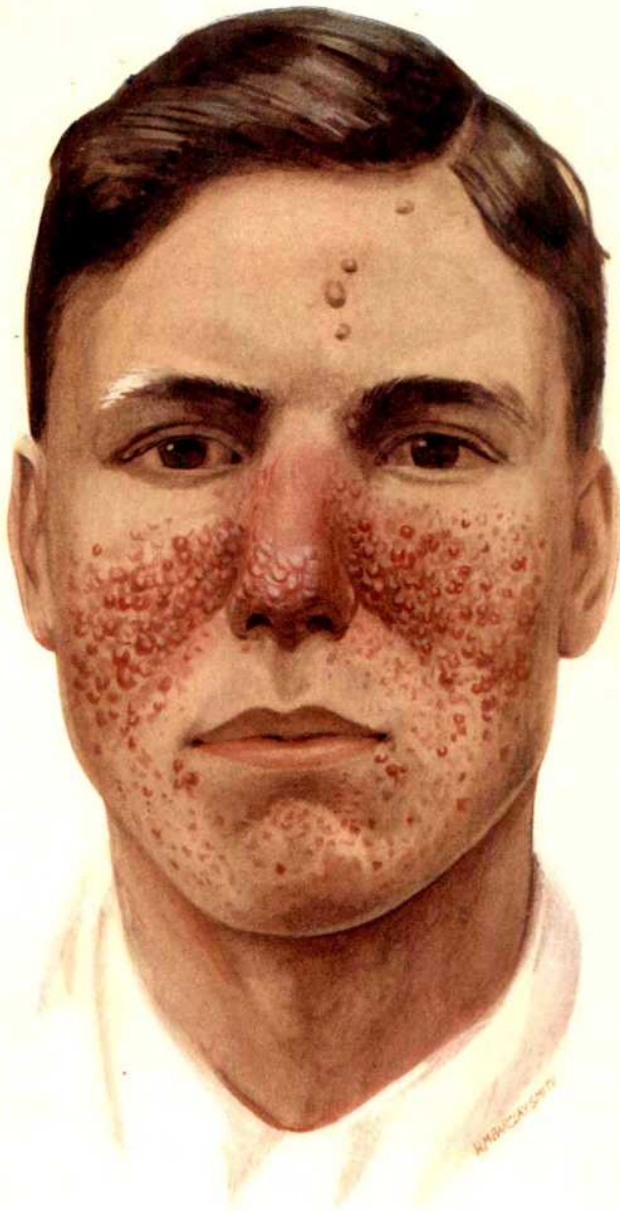
The clinical features of adenoma sebaceum comprise a nodular rash of red, yellowish-red or brownish colour distributed over a special region of the body. Thus it appears extensively over the face, showing itself first, according to Brushfield and Wyatt, in the naso-labial folds, later spreading so as to cover entirely the nose and the middle of the cheek over the infra-orbital region, in a butterfly-shaped area. The rash later spreads laterally but rarely shows itself inside the frontier of the naso-labial fold except to appear on the chin. Occasionally a few nodules are seen in the temples, or on the brow. In contrast to the florid redness of the nose and malar region, there is often a striking circumoral pallor.

The rash consists of numerous papules measuring on an average 4 mm. in diameter. They are somewhat hard in consistency and project above the skin for 2 to 5 mm. They are reddish in colour and at times translucent or jelly-like. They fade on pressure to a great extent, but may not do so entirely. Thus, in the centre a minute telangiectatic point or even a fine network of injected capillaries may be present. In certain areas, as for example over the tip and dorsum of the nose, the papules become confluent and form a smooth plateau of red shiny appearance, interspersed at times with telangiectases.

In Pringle's case the telangiectatic elements were rather striking, so that to-day many authors distinguish a "Pringle's type" of adenoma sebaceum from a "Balzer type," according to the degree of capillary injection. A third variety, spoken of as the "Hallopeau-Laredde" type, is sometimes described, consisting of vascular nodules of particular hardness from excessive fibrous tissue development.

It has often been noted that the facial lesions deepen in colour at the time of an epileptic attack and more especially during a succession of fits in cases of the serial type of epilepsy. Subjective symptoms are rare, though Pringle mentions that the rash may be painful in cold weather. Frequently the same area of skin is affected by an acne rosacea which waxes and wanes according to the state of the digestion and the proximity of a meal.

PLATE A.



Facial adenoma sebaceum in a case of epiloia.

To illustrate paper by Macdonald Critchley and C. J. C. Earl.

Microscopical examination, as shown by Pringle and others, reveals: (1) A thinning of the dermis; and (2) an extensive overgrowth of the sebaceous glands (see fig. 3). This histological structure leads some writers to imagine a neoplastic development of sebaceous glandular structure, a conception which is implied in the term "adenoma sebaceum," possibly allied to the so-called epithelioma sebaceum cysticum, but nowadays dermatologists usually regard adenoma sebaceum as a simple hypertrophy of the sebaceous glandular structure of the skin. According to Jadassohn, Poir and others, it more correctly belongs to the category of "sebaceous nævus."

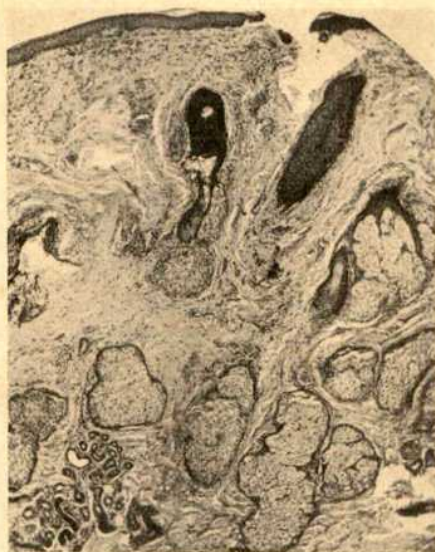


FIG. 3.—Histological appearance of a patch of adenoma sebaceum, taken from Case 24.
(Courtesy of Dr. Franklin.)

Adenoma sebaceum, though a very common accompaniment of tuberose sclerosis, is not invariably present. The earlier writers did not mention it specifically, and it is possible that its presence was ignored. Bonfigli, however, in describing his cases, stated definitely that no cutaneous affection was present. In our series, adenoma sebaceum was entirely absent from one case (No. 23) and was extremely slight in another (No. 10). It may be unrecognized by neurologists who perhaps attribute the facial appearance to the results of bromide medication.

A variety of adenoma sebaceum consists of a few discrete nodules, each no larger than a shot, scattered over the butterfly-area of the face

These differ from the typical papules in being pale and completely avascular; they never coalesce and there is no surrounding tissue-reaction. Indeed, the nodules may well escape cursory examination especially in artificial illumination; they are promptly recognized by their intense hardness when the pulp of the finger is lightly passed over the cheek. This particular variety is probably identical in the so-called "Balzer type"; it is rarer than the "Pringle type," occurring in four only of our series.

Fibromata.—Of the other cutaneous abnormalities, the commonest are small, flattened fibromata scattered over the trunk, particularly on the back. In at least ten out of our twenty-nine patients, fibromata were present. Usually they are multiple though numbering as a rule not more than a dozen. They vary in diameter up to 2 cm. They grow usually in the superficial layers of the skin, though once in our series a subcutaneous fibroma was found. In another of our patients several scalp fibromata occurred, each the size of a marble. Subungual fibromata have been recorded in this disease by Hintz [35] and by Busch [24].

A variant type of fibroma is one in which large numbers of miliary fibrous tubercles are scattered over the trunk. These are slightly raised papules, smaller than a pin's head; indistinguishable in colour from the surrounding skin; in size and appearance they resemble coarse "goose-flesh." This miliary type occurred in two of our patients and also in one recorded by Schuster. In Buschke's case, each seed-like milium was pierced by a lanugo-hair.

Another highly characteristic skin lesion is the so-called shagreen patch. This occurs as an uneven thickening of an area of skin, raising it a little above the surrounding surface. Each plaque is irregularly shaped and of about a palm's breadth. They are usually single and are commonest over the lumbo-sacral region. Their colour is that of the surrounding skin and may be discoverable only by close inspection or by palpation. Shagreen patches were found in four of our twenty-nine cases.

Pigmentary disorders are often present and take two main forms: first, a diffuse bronzing of wide regions of the skin; and, secondly, oval or circular areas of brown pigment, known as *café au lait* patches. These latter are indistinguishable from those met with in von Recklinghausen's disease.

At times a vitiligo-like arrangement is found, an area of pigmentation being abruptly succeeded by an area of abnormal whiteness. Such appearances are commonest upon the trunk, and there may exist an approximate segmental distribution recalling a thoracic dermatome (cf. Case 3).

Not infrequently patches occur which are of abnormal whiteness. They resemble in size and conformation the *café au lait* stains, but differ in absence of pigment instead of an excess. Lesions of this nature were found in two cases. Pigment may disappear from the hair in places, and in one of our patients a patch of local canities occurred on the outer half of one eyebrow.

In some patients there occurs over the neck or shoulders a cluster of small pedunculated dermal tags, varying in number from one to a score. This appearance of this *molluscum fibrosum pendulum* was encountered in two patients; in Case 9 they were particularly conspicuous (see fig. 1) and there is a striking resemblance to an illustration in Berg's paper of 1914.

Naevi are commonly described in cases of tuberose sclerosis, but were seen in two patients only in our series. Fox has reported a purpuric rash on the limbs and trunk.

Other simple and mixed types of cutaneous tumour have been recorded exceptionally in tuberose sclerosis; thus there are on record instances of lipoma (Dore [69]); fibromyolipoma (Kischer); angio-fibrolipoma (Bielschowsky).

Another rare cutaneous anomaly which has been recorded by Kreyenberg and his colleagues is a generalized hypertrichosis.

CHAPTER III.—MORBID ANATOMY.

CENTRAL NERVOUS SYSTEM.—The naked-eye appearance of the cerebrum presents characteristic features. It is not usual to find any obvious abnormality either in the cranium or in the meninges, although at times both these structures have been somewhat thickened. Ossification of the sutures has been noted at times. The pia-arachnoid usually strips easily. The cerebrum itself may be somewhat less than the normal in size and weight, though this smallness is never excessive. No marked disturbance occurs in the arrangement and disposition of the gyri, although it has been noted at times that the secondary and tertiary divisions of the sulci may be incomplete.

Characteristic of the disease is the presence in the convolutions of numbers of whitish, slightly prominent areas. These may occur in any part of the cerebral hemisphere, and there is no apparent area of predilection. In number they vary from one or two to twenty or thirty. They range in size from $\frac{1}{2}$ cm. broad and long, up to nodules measuring 2 cm. or 3 cm. in each dimension. The smaller areas are limited

to the conformation of a convolution, and are usually present upon the summit of a gyrus. The larger ones extend over two or three adjacent convolutions and may affect the depths of the sulci as well as the summits of the gyri. These areas are distinguishable from the surrounding cortex by a slightly paler tint; the contrast is not great, however, and the sclerotic regions are recognizable much less by inspection than by touch. On palpation of the hemispheres the affected regions are at once betrayed by their firm consistency, giving rise to a hardness which has been likened to cartilage, rubber or potato (hence

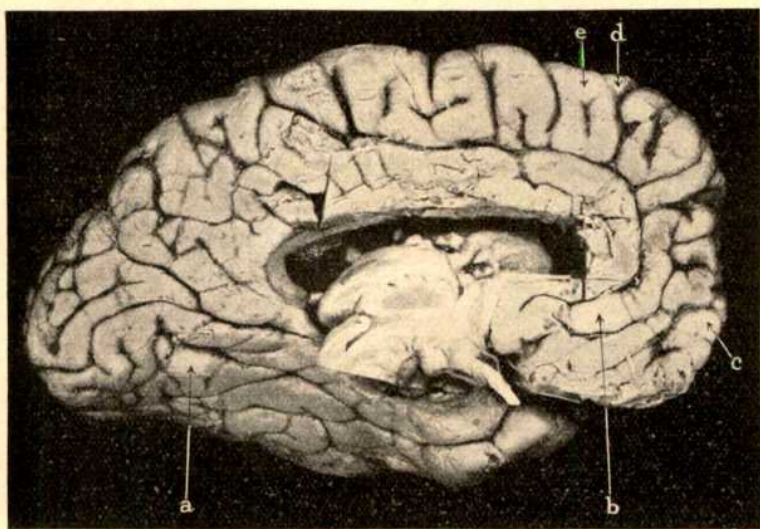


FIG. 4.—Mesial aspect of the left hemisphere from a case of tuberose sclerosis. Areas of sclerosis are marked a, b, c, d, e. Note also the "candle-gutterings" in the lateral ventricle.

"tuberose"). Palpation frequently reveals smaller and darker nodules which escape even careful scrutiny.

At times some of the larger sclerotic areas are umbilicated, but this is, on the whole, exceptional. Pellizzi has distinguished two types of sclerotic nodules according to their macroscopic appearance. In the one, elongated tubera lie along the course of a gyrus, while in the other more sharply demarcated, circular areas stretch from one convolution to another. The surface in the first type is usually smooth, convex, or slightly flattened, while in the second variety the surface may be somewhat roughened and also umbilicated.

Cross-section through the hemispheres displays more clearly the distribution and appearances of the foci (fig. 5). The relative pallor

of the affected grey matter is striking. At times the sclerotic nodules degenerate in their centre so as to form small cysts; more commonly minute calcareous fragments are encountered within the foci.

The cerebral hemispheres are usually the sole region of the central nervous system affected. In exceptional instances tubera have been described in the cerebellum (Brückner; Vogt, Case 3), the medulla (Geitlin), the spinal cord (Perusini) and the retina (van der Hoeve; Feriz).

In the walls of the third and lateral ventricles, immediately beneath the ependyma, small irregular projections are found, arising usually

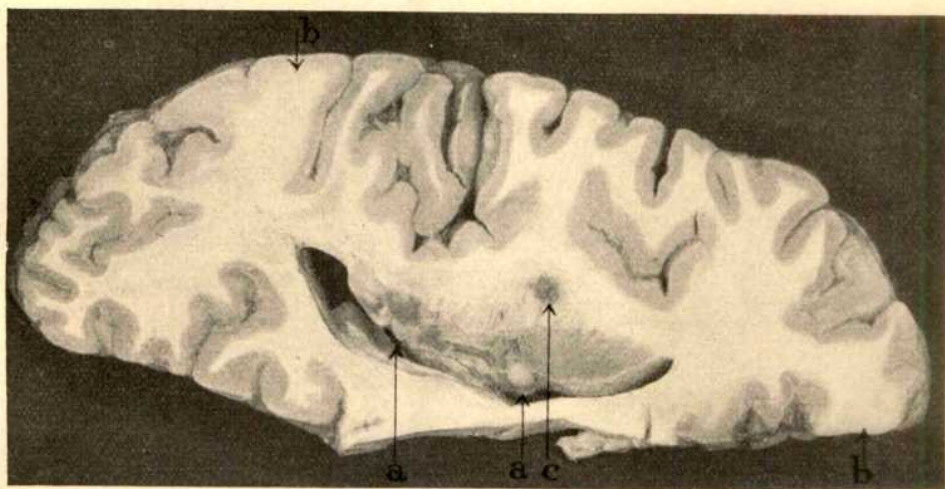


FIG. 5.—Cross-section of a hemisphere; a, "candle gutterings" in the wall of the lateral ventricle; b, cortical tuberoze patches; c, patch of sclerosis in the white matter.

from the thalamus. These appear as tiny, button-like tumours, or, in larger examples, as "candle-gutterings" (Lind) running from above downwards and following (Campbell) the tributaries of the vein of the corpus striatum (figs. 5 and 6).

Microscopical appearance.—The histological structure of these sclerotic zones in the cortical and subependymal grey matter comprises broadly a marked anarchy in the stratification of the nerve-cells with regressive changes in the neurones themselves; considerable overgrowth of glia cells and their processes, and the appearance of curious large cells of a type foreign to the mature nervous system. Each of these processes warrants detailed study and description. Although the tubera appear to the naked eye as sharply-demarcated regions, it becomes obvious from microscopical examination that no abrupt transition exists

between healthy and diseased areas. On the contrary, it is found that one zone merges gradually into the other.

In addition to the macroscopic foci themselves, the intervening and apparently healthy regions demand attention. Histological investigation of the cortical zones around and between the foci shows changes of a profound character differing merely in degree from those in the tubera. Furthermore, alterations of a microscopic character may usually be

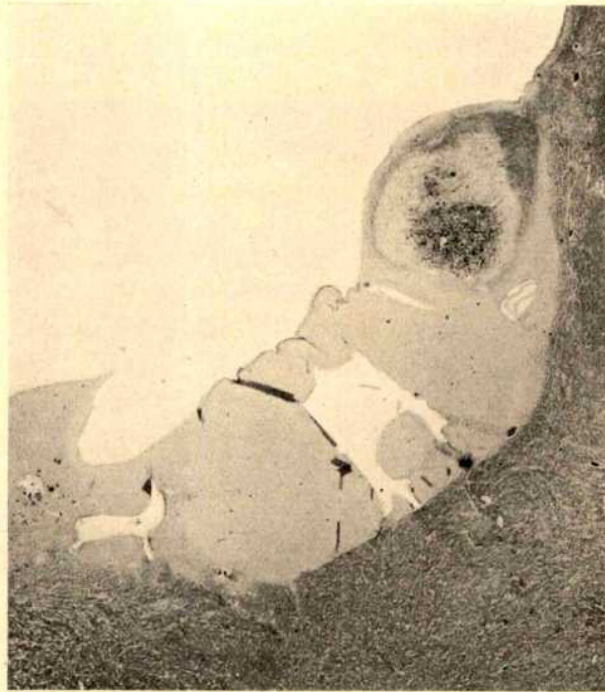


FIG. 6.—Section of the wall of a lateral ventricle to show the appearance of "candle gutterings" in cross section.

revealed within other regions of the central nervous system, and particularly in the cerebellum and in the spinal cord. The morbid process active in cases of tuberosc sclerosis is, therefore, much more diffuse than the naked-eye examination would suggest.

Nerve-cell changes within the foci.—Portions of cortex stained by Nissl, Bielschowsky and hæmatoxylin-van Gieson methods, show a relative pallor in the sclerotic zones. Under the microscope the individual cell laminæ cannot be demonstrated. Pyramidal cells may be present in the more superficial layers, and granular elements may be

seen scattered among the larger neurones of the deeper parts. The orientation of the pyramidal cells may be altered so that the bases are no longer directed downwards and the apices upwards.

The total number of cellular components is somewhat reduced, and the morphological state of many of the cells is changed. Thus, one may observe alterations in the outline, with clumping and later disappearance of the Nissl granules and a lateral position of the nucleus. Thickening of the processes may occur, and the cell as a whole become shrunken. Fatty degeneration is present, though not in profound degree.

Silver-staining methods may show the intracellular fibrillary network heavily impregnated with silver deposits so as to recall strikingly the Alzheimer cell changes seen in senile dementia. This resemblance is enhanced by the occasional appearance of argentophil depositions arranged in an annular fashion, not unlike the appearance of a very early senile plaque.

Glial alterations—A marked proliferation of the neuroglia constitutes one of the outstanding features, and is betrayed by the density of the affected zones in sections stained by the Victoria blue or Mallory method. There is a considerable overgrowth of glia fibrils which are mainly of the thin type. At times, however, the fibres may be of such thickness as to belie their glial character, and Campbell mistakenly described them as fibrous in type. The proliferation is most marked in the cortex, though it extends for some distance into the underlying white matter. Peculiar interlacing arrangements of the fibres are described and likened to "crossed-swords," or "ruffled-hair"; arrangements of this type are conspicuous in the more superficial zones of a sclerotic focus. No increased density of the glia is seen around the blood-vessels.

In the subependymal growths the neuroglial fibrillary proliferation produces a loosely interlacing complex of parallel strands. The ependymal covering remains intact, and between this layer and the glial overgrowth is an interval occupied by loose areolar tissue; in this zone a venule may run, according to Campbell, but in none of our sections was this feature apparent.

A less obvious increase in the number of neuroglial cells is seen, and large astrocytes are frequent. No conspicuous overgrowth of microglia takes place, though Bolsi [12] described a perivascular proliferation of the Hortega cells. Qualitative changes in the glia occur and they frequently respond to staining methods such as that of Bielschowsky, to which ordinarily they do not react.

At times glial proliferation takes on such a localized and excessive type of overgrowth as to show itself on naked-eye inspection as a definite tumour-like mass. Such a condition appears exclusively in the intraventricular growths, and small tumours may develop up to the size of a walnut and may be accompanied during life by symptoms of raised intracranial pressure. The histological structure is always that of glial tissue, but individual cases vary according to the proportion of cellular or fibrillary elements. Thus, in the original case of Hartdegen the term "glioma gangliocellulare" was applied; Brushfield and Wyatt refer to the large nodule in their fatal case as a "glioma," and specify that it was composed chiefly of slender spindle-shaped cells with long



FIG. 7.—Microscopical appearance of a gliomatous tumour in a case of tuberose sclerosis.

interlacing processes, forming bands and whorls of fairly open tissue and containing in their meshes numerous thin-walled capillaries and free red blood-corpuscles. In Schuster's case two conspicuous intraventricular tumours were encountered; the larger one, the size of a plum, consisted in a gliomatous mass of large cells, fibres being entirely absent. Many of the constituent cells possessed a homogeneous protoplasm and many nuclei. A case recorded by Bielschowsky and Berliner revealed, in addition to numerous foci of tuberose sclerosis, an intraventricular neoplasm the size of a "plumpit." The histological picture was that of a tumour formed of proliferating blastomatous cells; no concretions were found as in the case of the other "candle-gutterings." The authors believe that the neoplasm was of more recent date, and they speculate as to whether or not this new growth began to develop

on the basis of a previously existing old nodule. According to Globus [33], the glial paraventricular tumours belong to the group of spongioblastoma multiforme. In McConnell's case of gliomatous tumour associated with tuberoze sclerosis, the histological picture is that of a large-celled astrocytoma (see fig. 7).

Giant cells.—Perhaps the most striking and the most important feature is the presence of abnormal cells of large size in relation with the sclerotic foci. Since Hartdegen's original description, they have been noted by all writers on the pathology of tuberoze sclerosis, and have occasioned much discussion as to their nature and their bearing upon our conception of tuberoze sclerosis in general.

These cells lie typically in the depths of the sclerotic nodules, i.e., where the neuronie and glial changes are most intense. Both cortical and subependymal tubera may contain such cells, though they are more numerous in the former situation. It is important to realize, however, that they may occur outside of the cerebral cortex; thus they appear as heterotopies in the white matter near the tubera. Furthermore, they may be demonstrable in the cortex away from the sclerotic regions, and they have also been noted in more remote portions of the nervous system such as the cerebellum, medulla and spinal cord.

Much controversy has arisen as to the nature of these large cells, and in particular as to whether they are derivatives of glial or nerve elements. It appears definite, however, from careful histological study that all the large cells of a particular case do not possess the same morphological and staining characters and probably represent entirely different cells, their sole common feature being their large size. A study of the personally observed specimens bears out what seems to be the tendency of modern histological opinion, namely, that the large cells are of varying appearances, but tend to approximate either to the nerve-cell or to the glia-cell type. All manner of transition forms link up these extremes.

In this way we may distinguish: (1) a large cell of neuronie type; and (2) a large cell with glial resemblance.

(1) *Large cells approximating to the neuronie-cell type.*—These usually preponderate slightly, and are more numerous in the cortical than in the subependymal growths. They are well demonstrated by the ordinary nerve-cell stains and particularly by Bielschowsky's method; they do not react to glial stains. In size, they vary from a large pyramidal cell up to that of a Betz ganglion cell; and when secondary changes occur, further distension may increase their bulk still more.

As a rule they occur in clusters of three or more, and may be surrounded by some densification of the glia. They are occasionally triangular or polyhedral in outline, but the larger specimens are elliptical or even circular.

The internal structure of these cells shows various abnormalities in the position and staining reactions of the nuclei. Considerable variability exists in the character of the processes; sometimes they are short and thick, and at times a stem arises which quickly breaks up into finer branches. Globus has illustrated a giant cell of this type with a very long and tape-like process, extending through several microscopic fields.



FIG. 8.

The neuron character of this type of giant cell is suggested by the presence of intracellular fibrillary network and also of Nissl (tigroid) granules.

(2) *Large cells of glia type.*—Cells of this order are somewhat less numerous than the others and occur more particularly in the ventricular nodules. They are also grouped in the vicinity of blood-vessels, to the walls of which they may be attached. Their shape is unlike that of a nerve-cell, being oval or circular. There are no intracellular fibrillæ or granules, and the processes are invisible except in silver-stained preparations. With such methods the processes are displayed, sometimes recalling those of a nerve-cell, but at other times numerous short and curly processes radiate at intervals from the periphery.

Other changes which may be present within the sclerotic regions include alterations in the blood-vessels; several writers have drawn attention to a dilatation of the vessels which may attain sinusoid proportions. Hyaline degeneration within the vessel walls, affecting especially the adventitia, has also been described. In many instances, however, changes in the blood-vessels are slight or absent.

Deposits of calcium salts or of hyaline material are often seen lying amid the whorls of glial fibrils, especially in the ventricular nodules.

Although the lesions of tuberose sclerosis are most marked in the



FIG. 9.



FIG. 10.

cortical or subependymal grey matter, they may occasionally occur in the central grey masses of the brain. Thus, in two cases of Bielschowsky and Freund [9], changes similar to those in the cortex were spread over the basal ganglia, affecting the caudatum chiefly and the putamen to a lesser extent. The globus pallidus was only slightly implicated.

Changes in the cerebellum have been described, but are uncommon. In our cases no abnormality was present. Pollak [54] found atypical giant cells in the cerebellum; abnormal ganglion cells were also seen by de Montet. Orzechowski and Nowicki [50], and Brushfield and Wyatt, mentioned a slight reduction in the number of Purkinje cells. The glia cells may be increased in number. Von Meduna [67] described in his case a reduplication of the granular layer in the cerebellar cortex.

Nodular lesions within the cerebellum appear to be still rarer. Bielschowsky found macroscopic lesions here in one case only out of twelve. In this case there were localized lesions typical of tuberose sclerosis lying in the white matter of the cerebellar hemispheres, and demarcated in an unusually sharp manner from the surrounding tissue. Otherwise the cerebellar cortex showed little in addition to a parenchymatous atrophy with glial replacement, and the appearance recalled that seen in juvenile paresis or the heredo-ataxias. Only an occasional large cell betrayed the diagnosis.

The heart.—The cardiac anomaly classically associated with tuberose sclerosis is rhabdomyoma. The condition is a rare one, only forty-two cases having been reported. In thirty-two cases there was a note as to the condition of the brain, and in no fewer than twenty-five of these cases tuberose sclerosis was present (Furber). Ten cases had kidney tumours, tuberose sclerosis, and cardiac rhabdomyomata.

The tumours are usually small and multiple, appearing as greyish rounded masses, sometimes embedded in the muscle itself and sometimes projecting into the cavity of the heart. The commonest sites are the septum, trabeculæ, papillary muscles and anterior wall, and the tumours lie usually immediately beneath the endocardium. Microscopically they consist of irregularly arranged striated cells of primitive type varying from 50 to 200 μ in diameter (Wolbach [65]) and having nuclei varying in number from one to four. The tissue is honey-combed with wide vacuolated spaces containing glycogen (Rehder [57], Mönckeberg [47]).

Steinbiss [62] finds that these tumours undergo fibrosis and never show malignant changes. Their exact nature is a little obscure. They are evidently of prenatal origin, and metaplastic rather than neoplastic in nature.

The cardiac findings in Case 15 of our series are worth recording. The boy was known to have an enlarged heart, and a diagnosis of aortic stenosis with incompetence had been made. Autopsy showed the heart weighed 23 ozs. Subaortic stenosis of congenital type was present, a dense membrane running round the aortic vestibule immediately below the base of the valve and narrowing the orifice to $\frac{1}{2}$ cm. In addition, the whole of the papillary muscle and trabeculæ of the left ventricle were shrunken and fibrosed, the process extending for 3 mm. into the heart wall. Microscopy showed fibrous tissue only, and sections from various other portions of the wall revealed no abnormality. The endocardium and pericardium were both normal.

Kidneys.—Renal tumours are found in about 80 per cent. of cases of tuberose sclerosis. They are rarely diagnosed in life, though in Hyman's case nephrectomy was necessary—a large necrotic hypernephroma being removed. In our series no renal signs have been observed during life.

The tumours are usually multiple and bilateral and vary in size from a pin-head to a large orange. They are nearly always cortical, and though not encapsulated they are sharply demarcated. They rarely, if ever, form metastases.

Histologically they are of embryonal mixed type, the precise appearance varying from case to case. Thus angiosarcoma, liposarcoma, myosarcoma, myolipoma, fibrolipoma, perithelioma, and hypernephroma have all been described.

Of those four cases in our series which have come to post mortem multiple kidney tumours were found in each. In Cases 15 and 17 they were classified as peritheliomata, whilst in Case 5 the tumours were of primitive mixed sarcomatous type, and one the size of a walnut had become necrotic.

Duodenum.—Duodenal tumours have been described in one case (Sailer [58]). At autopsy upon an epileptic idiot, aged 15, a number of small nodules were found in the wall of the duodenum; microscopically these growths were necrotic and structureless in their central part with small round cells at the periphery. They were considered to be sarcomatous in nature. Adeno-sarcomata were found in both kidneys.

CHAPTER IV.—CLINICAL VARIANTS.

With fuller knowledge of the varied aspects under which tuberose sclerosis presents itself, the problem arises as to the status of the numerous atypical and incomplete forms.

Examination of the relatives of epileptic subjects suggests that we are justified in regarding the following as probably representing incomplete forms of tuberose sclerosis:—

- (1) Adenoma sebaceum alone.
- (2) Adenoma sebaceum with epilepsy but no mental change.
- (3) Adenoma sebaceum with symptoms of cerebral tumour.
- (4) Visceral tumour alone (including retinal tumours).

Our present conception of this aspect of tuberose sclerosis is necessarily very elastic, and until we have more pathological data most of our ideas will remain conjectural.

(1) The first important variant concerns the finding of adenoma sebaceum alone. Dermatologists are familiar with this condition occurring in individuals of normal intelligence who have never suffered from epilepsy and who show no neurological abnormality whatever. It is arguable, of course, that such patients only rarely come before the neurologist and that slight nervous or mental changes might be present though not obvious on cursory examination. Such an opinion, though probably correct in many instances, does not apply to cases, for example, where close co-operation has existed between neurological and dermatological departments.

The question arises whether histological changes occur in the brain of individuals who during life have shown adenoma sebaceum alone. It is not unlikely, from our knowledge of tuberose sclerosis, that slight alterations might be found in the cortex of such individuals, differing only in degree from those occurring in epiloia. As far as we have been able to trace, no record is available of the cerebral findings in a case of isolated adenoma sebaceum.

The possibility of latent cerebral changes existing in patients with simple adenoma sebaceum is further borne out by the occasional development of insanity in middle-life in cases which up to then were of dermatological interest only.

(2) The following case report illustrates the co-existence of epilepsy with facial adenoma sebaceum in an individual of normal intelligence.

Case 24.—A. C., female, first attended the out-patient department of the National Hospital, Queen Square (Dr. C. P. Symonds) on account of epileptic fits, in February, 1927, being then 29 years of age. Her parents had died in her infancy, the father having been insane. She was the third of five children; her eldest brother suffered from fits and died in an asylum at the age of 30. The others are healthy, one sister is married and has a healthy child. No family history of adenoma sebaceum was obtainable. When the patient was 8 years old, adenoma sebaceum appeared on the face, and she had her first fit. From the ages of 14 to 21 no attacks occurred, but they recurred and persisted at irregular intervals. She attended the National Hospital for six months and then left to get married. She had one premature child which was born dead. She was referred again to one of us (M. C.) in the out-patient department of the National Hospital by the kindness of Dr. John Franklin who had been attending her for eczema of the nipples. She was at this time aged 33. On examination no neurological abnormality was found. She appeared of normal intelligence and is at present earning her living as an upper domestic. Facial adenoma sebaceum was present, of a comparatively avascular type; a portion of the affected skin was excised by Dr. Franklin for histological examination (see fig. 3). Apart from eczema of the nipples,

there were no other cutaneous lesions. No stigmata of degeneration except syndactyly of the second and third toes of both feet.

Here, a psychopathic family history strengthens the view of a relationship with tuberose sclerosis. It is probable that histological changes exist in the cerebrum, slight in degree but qualitatively identical with those in the complete forms of tuberose sclerosis.

(3) Schuster's first case exemplifies another clinical variant. An epileptic patient, of normal intellect, suffering also from adenoma sebaceum, developed in early adult life signs of intracranial hypertension. The autopsy revealed, in addition to the ordinary findings of tuberose sclerosis, the presence of an intracerebral glioma. Similar case reports have been made by Kaufmann and Fischer, and by Bychowski.

(4) The presence of primitive visceral tumours alone, without accompanying mental or nervous abnormalities and without adenoma sebaceum, may under certain circumstances constitute a *forme fruste* of tuberose sclerosis. Reference has already been made to Berg's case, where a child and her father both died with renal tumours and cerebral tuberose sclerosis; the grandfather died after operation for renal tumour. During life he had shown no evidence of neurological disorder, and there had been no adenoma sebaceum. We do not know, however, whether any histological changes were present in the cerebrum. Other cases are on record in which an individual, otherwise normal, has been under the care of an urological surgeon for a renal tumour, and where at post-mortem examination typical cerebral changes were discovered.

A certain number of pathological reports are on record of multiple rhabdomyomata of the heart associated with cerebral sclerosis. Unfortunately we do not know sufficient of the clinical picture to determine whether the cases were examples of complete tuberose sclerosis.

It is certain that the retinal tumours may occur without accompanying cutaneous mental or physical changes. Thus, van der Hoeve found a retinal tumour in the fundus of a patient aged 21, who showed no other abnormalities. The nature of the tumour was revealed when investigation of the family history discovered five brothers and sisters suffering from advanced tuberose sclerosis.

CHAPTER V.—THE NATURE OF TUBEROSE SCLEROSIS;
RELATIONSHIP WITH VON RECKLINGHAUSEN'S DISEASE.

The nature of tuberoses sclerosis is still in doubt, but there is an increasing evidence to suggest a developmental anomaly commencing early in foetal life. Older views were soon set aside; thus Scarpatetti's theory of tuberoses sclerosis as a manifestation of inherited syphilis, and Fürstner and Stühlinger's conception of a foetal leptomeningitis, were never sustained.

Most of the recent disharmony concerns the view taken of the nature of the pathological changes and particularly of the giant cells. Bielschowsky has tended to regard them as reactive compensatory formations consequent upon a primary glial hyperplasia. Most histologists, however, regard the giant cells as of duplex character and suggest that they represent a primitive type of cell not far removed from an undifferentiated neuroblast; they may develop characteristics which are either glial or neuronie.

Thus two views emerge as to pathogenesis. On the one hand tuberoses sclerosis may be regarded as essentially a hyperplastic disorder of the neuroglia, originating during embryonic life and associated with hyperplasias in other extraneural structures. Thus Bielschowsky regarded the condition as comprising a "blastomatous growth-tendency of the spongiocyte." On the other hand, the view is held of a widespread metaplasia, affecting mainly the ectodermal tissues, but also to some extent mesodermal and endodermal derivatives, having its beginnings in utero. According to Feriz [30] tuberoses sclerosis is a disorder of differentiation between parenchymatous and supporting tissues, leading to exaggerated and localized overgrowths.

An association between tuberoses sclerosis and von Recklinghausen's disease has been emphasized within the past twenty years. Points of contact between the two disorders are seen firstly in the similarity of certain clinical features. Both disorders are characterized by striking cutaneous anomalies, and more particularly by pigmentary disorders, *café au lait* patches, fibromata, nævi. Both are heredo-familial affections often associated with psychopathic trends. Epilepsy is associated with both, though rare in von Recklinghausen's disease. In both conditions retinal tumours of identical appearance may be demonstrable.

The other suggestive line of argument concerns those rare but important cases in which marks of tuberoses sclerosis have co-existed with those of a neurofibromatosis.

A curious and important case recorded by Orzechowski and Nowicki was that of a male patient of 18, in whom there were found at autopsy changes typical of tuberose sclerosis; in addition there occurred a centrally-placed neuro-epithelioma of the cord and medulla; a neuroma in the choroid plexus of the third ventricle; two tumours arising in the blood-vessel walls in the cortex; proliferative changes in the cells of the sheath of Schwann in the spinal roots and in the peripheral and cranial nerves; a similar growth in the muscular coat of the stomach; and a fibro-endothelioma of the dura mater. The authors regarded their case as indicating the identity of neurofibromatosis and tuberose sclerosis, the final picture depending merely upon the particular location of the morbid process. Orzechowski and Nowicki suggested that tuberose sclerosis should be renamed "neurinomatosis centralis," that peripheral neurofibromatosis should be spoken of as "neurinomatosis peripherica," and that the term "neurinomatosis universalis" should apply to cases like their own, in which the two disorders are associated.

A few other cases of this association are on record. Thus, Perdrau [64] is said to have demonstrated neurofibromatous growths in the kidney in a case of tuberose sclerosis. In Gamper's case [32] a patient dying with generalized von Recklinghausen's disease showed at autopsy numerous interesting anomalies within the central nervous system. These included two "neurinomatous" growths lying under the ependyma; multiple ventricular tumours of glial origin; sclerosis and blastomatous cell proliferation with demyelination in the frontal lobes and in the vermis; circumscribed nodules in the cerebellar hemispheres. In a case of tuberose sclerosis mentioned by Globus a "neurofibroma conforming to the central type" was attached to the bundle of Vicq D'Azyr.

Various authors have pointed out the identity of certain of the cerebral appearances in tuberose sclerosis and in von Recklinghausen's disease. Thus, in both conditions there may be seen hyalin thickenings in the vessel walls (Feriz); abnormal monster cells (Bielschowsky); similar histological changes in the cerebellum (Maas, Orzechowski and Nowicki).

Van der Hoeve, who called attention to the presence of retinal tumours in tuberose sclerosis, pointed out that identical masses (or phakomata) may occur in cases of von Recklinghausen's disease. He, too, suggests a change in terminology, and would designate tuberose sclerosis as "phakomatosis Bourneville," and neurofibromatosis as "phakomatosis Recklinghausen."

It must be pointed out that the occurrence of cases of these mixed types is very exceptional and that the points of resemblance largely hinge upon the central changes in neurofibromatosis, a feature which in itself is rare. We feel that the similarities between tuberose sclerosis and von Recklinghausen's disease have perhaps been rather over-emphasized.

BIBLIOGRAPHY.

- [1] BABONNEIX, L. "À propos de l'épilepsie," *Arch. de Méd. des. Enf.*, 1928, **31**, 188.
- [2] BALZER, F., and MÄNTRIER, P. "Étude sur un cas d'adénomes sébaces de la face et du cuir chevelu," *Arch. de Physiol.*, 1885, **6**, 564.
- [3] BALZER, F., and GRANDHOMME. "Nouveau cas d'adénomes de la face," *ibid.*, 1886, **8**, 93.
- [4] BERG, H. "Vererbung der tuberöse Sklerose durch zwei bzw. drei Generationen," *Zeit. f. d. g. Neur. u. Psych.*, 1913, **19**, 528.
- [5] *Idem.* "Ueber die klinische Diagnose der tuberöse Sklerose und ihre Beziehungen zur Neurofibromatosis," *ibid.*, **25**, 229.
- [6] BIBLSCHOWSKY, M., and GALLUS. "Ueber tuberöse Sklerose," *Journ. f. Psych. u. Neur.*, 1913, **20**, 1.
- [7] *Idem.* "Ueber tuberöse Sklerose und ihre Beziehungen zu Recklinghausenscher Krankheit," *Zeit. f. d. g. Neur. u. Psych.*, 1914, **26**, 188.
- [8] *Idem.* "Zur Histopathologie und Pathogenese der tuberösen Sklerose," *Journ. f. Psych. u. Neur.*, 1924, **30**, 167.
- [9] *Idem.* und FREUND. "Ueber Veränderungen des Striatums bei tuberöser Sklerose und deren Beziehungen zur den Befunden bei anderen Erkrankungen dieses Hirnteils," *ibid.*, 1918, **24**, 20.
- [10] BIBLSCHOWSKY, M., and ROSE, M. "Zur Kenntnis der zentralen Veränderungen bei Recklinghausenscher Krankheit," *ibid.*, 1927, **35**, 42.
- [11] BLOCK, E. BATES. "Epilepsia, adenoma sebaceum with epilepsy," *Internat. Clinics*, 1931, **3**, **41**, 218.
- [12] BOLSI, D. "Contributi all'istologia patologica cerebrale della Sclerosi tuberosa," *Riv. di Pat. Nerv. e Ment.*, 1928, **33**, 656.
- [13] BOURNEVILLE. "Scléreuse tubéreuse des circonvolutions cérébrales; idiotie et épilepsie hémiplegique," *Arch. de Neur.*, 1880-81, **1**, 81.
- [14] *Idem.* "Scléreuse cérébrale hypertrophique ou tubéreuse compliquée de méningite," *Le Progr. méd.*, 1896, 3me., Serie 3, 129.
- [15] *Idem.* "Idiotie symptomatique de scléreuse tubéreuse ou hypertrophique," *Recherches, etc.*, 1899, **19**, 188.
- [16] *Idem.* "Idiotie symptomatique de scléreuse tubéreuse ou hypertrophique," *Le Progr. méd.*, 1889, **3**, **10**, 241.
- [17] *Idem.* "Idiotie et épilepsie symptomatique de scléreuse tubéreuse ou hypertrophique," *Arch. de Neur.*, 1900, **11**, 29.
- [18] *Idem.* "Recherches cliniques et thérapeutiques sur l'épilepsie, l'hystérie et l'idiotie," Paris, 1881, **1**, 3.
- [19] BOURNEVILLE and BONNABRE. "Idiotie complète; vertiges et accès épileptiques; rougeole; bronchio-pneumonie consécutive; scléreuse tubéreuse des circonvolutions cérébrales," *Le Progr. méd.*, 1881, **9**, 667.
- [20] *Idem.* "Scléreuse tubéreuse ou hypertrophique des circonvolutions. Idiotie complète," *ibid.*, 1881, **9**, 1007.
- [21] *Idem.* "Scléreuse tubéreuse ou hypertrophique des circonvolutions cérébrales," *Bull. Soc. Anat.*, 1881, **1**, 545.
- [22] BOURNEVILLE, D. M., and BRISSAUD. "Encéphalite ou scléreuse tubéreuse des circonvolutions cérébrales," *Arch. de Neur.*, 1880-81, **1**, 897.

- [23] BRUSHFIELD, T., and WYATT, W. "Epiloia," *Brit. Journ. Child. Dis.*, 1926, **23**, 178 and 264.
- [24] BUSCH, N. "Morbus Pringle: Subunguale Fibromatose. Papillomatosis cutis et mucosae. Mollusum pendulum," *Dermat. Zentralbl.*, 1931, **62**, 8.
- [25] BYCHOWSKI, Z. "Zur Klinik der Sklerosis tuberosa," *Deut. Zeit. f. Nerv.*, 1931, **120**, 304.
- [26] CAMPBELL, A. W. "Cerebral Sclerosis," *Brain*, 1905, **28**, 867.
- [27] CREUTZFELDT. "Zur Frage der tuberöse Sklerose," *Zentralbl. f. d. ges. Neur. u. Psych.*, 1932, **62**, 396.
- [28] DOBSON, M. B. "A Case of Epileptic Idiocy Associated with Tuberous Sclerosis of the Brain," *Lancet*, 1906, **2**, 1583.
- [29] FURBER, S. "Congenital Rhabdomyoma of the Heart," *Amer. Journ. Path.*, 1931, **7**, 105.
- [30] FERIZ, H. "Ein Beitrag zur Histopathologie der tuberöse Sklerose," *Virchow's Arch.*, 1930, **278**, 690.
- [31] FOWLER, J. S., and CARNEGIE DICKSON, W. H. *Lancet*, 1910, **1**, 1851.
- [32] GAMPER, E. "Zur Kenntnis der zentralen Veränderungen bei Morbus Recklinghausen," *Journ. f. Psych. u. Neur.*, 1928, **39**, 89.
- [33] GLOBUS, J. H. Article on Malformations of the Nerve Cell in "Cytology and Cellular Pathology of the Nervous System," 1932, vol. iii, p. 1150.
- [34] HARTDEGEN, A. "Ein Fall von multipler Verhärtung des Grosshirns nebst histologisch eigenartigen harten Geschwülsten der Seitenventrikel ('Glioma gangliocellulare') bei einem Neugeborenen," *Arch. f. Psych.*, 1881, **11**, 147.
- [35] HINTZ, A. "Ein Fall von Naevus Pringle und Neurofibromatosis (V. Recklinghausen)," *Arch. f. Derm. u. Syph.*, 1911, **106**, 277.
- [36] VAN DER HOEVE, J. "Augengeschwülste bei der tuberösen Hirnsklerose (Bourneville) und verwandten Krankheiten," *Arch. f. Ophthalm.*, 1923, **111**, 1.
- [37] *Idem*. "Eye Diseases in Tuberose Sclerosis of the Brain and in Recklinghausen's Disease," *Trans. Ophthal. Soc. (Lond.)*, 1923, **43**, 534.
- [38] HYMAN, A. "The Association of Hypernephroma with Tuberose Brain Sclerosis and Adenoma Sebaceum," *Journ. of Urol.*, 1922, **8**, 317.
- [39] JAKOB, A. "Zur Pathologie der Epilepsie," *Zeit. f. d. g. Neur. u. Psych.*, 1914, **15**, 1.
- [40] JAMIESON, W. A., and HUIE, L. H. "Mollusum Fibrosum Pendulum and Adenoma Sebaceum," *Brit. Journ. Derm.*, 1906, **18**, 379.
- [41] JOSEPHY, H. "Zur Pathologie der tuberöse Sklerose," *Zeit. f. d. g. Neur. u. Psych.*, 1921, **67**, 232.
- [42] KIRPICHNIK, J. "Ein Fall von tuberöser Sklerose und gleichzeitigen multiplen Nierengeschwülsten," *Virchow's Arch.*, 1910, **202**, 358.
- [43] KREYENBERG, E., DELBANC, E. and HAAK, K. "Beiträge zur Klinik und Variationsbreite der tuberöse Sklerose unter besonderer Berücksichtigung des Adenoma sebaceum," *Zeit. f. d. g. Neur. u. Psych.*, 1930, **123**, 236.
- [44] LÁZÁR, K. *Gyógyászat*, 1931, **1**, 404. Abs. in *Ztbl. f. d. ges. Neur. u. Psych.*, 1932, **63**, 67.
- [45] LEX, A. "Sur la sclérose tubéreuse des circonvolutions cérébrales," *Journ. de Neur.*, 1931, **31**, 689.
- [46] LIND, W. A. T. "Epiloia," *Med. Journ. Austral.*, 1924, **2**, 290.
- [47] MONCKEBERG. "Multiple Rhabdomyome des Herzens," *Munch. med. Woch.*, 1914, **61** (2), 2108.
- [48] DE MONTET, CH. "Recherches sur la Sclérose tubéreuse," *L'Enc.*, 1908, **3** (1), 97.
- [49] NITSCH, M. "Augenhintergrundsbefund bei tuberöser Hirnsklerose," *Zeit. f. Augenheilk.*, 1927, **62**, 78.
- [50] ORzechowski, K., and NOWICKI, W. "Zur Pathogenese und pathologischer Anatomie der multiplen Neurofibromatose und der Sclerosis tuberosa (Neurofibromatosis universalis)," *Zeit. f. d. g. Neur. u. Psych.*, 1912, **11**, 237.
- [51] PELAGATTI. *Ann. de Derm. et de Syph.*, 1904, 988. (Abs. *Brit. Journ. Derm.*, 1905, **17**, 342.)

- [52] PELLIZZI. "Contributo allo studio del idiozia," *Riv. sperim. di Frenat.*, 1901, **27**, 265.
- [53] PERUSINI. "Ueber einen Fall von Sclerosis tuberosa hypertrophica (Istiotipia corticale disseminata von Pelizzi)," *Monat. f. Psych. u. Neur.*, 1905, **17**, 169, 255, 352.
- [54] POLLAK, E. "Ueber tuberosa Hirnsklerose," *Obstetner's Arb.*, 1928, **24**, 98.
- [55] PRINGLE, J. J. "A Case of Congenital Adenoma Sebaceum," *Brit. Journ. Derm.*, 1890, **2**, 1.
- [56] V. RECKLINGHAUSEN. *Verhandl. Berl. Gesell. f. Geburtshilfe*, 1868, **15**, 75. (Cited by HARTDEGEN.)
- [57] REHDER. *Vichow's Archiv*, 1914, **217**, 174.
- [58] SAILER, J. "Hypertrophic Nodular Sclerosis," *Journ. Nerv. and Ment. Dis.*, 1898, **25**, 402.
- [59] SCHUSTER, P. "Die Beziehungen der sog. tuberosa Sklerose des Gehirns zur Dermatologie," *Dermat. Wochenschr.*, 1913, **57**, 1475.
- [60] *Idem.* "Beitrage zur Klinik der tuberosen Sklerose des Gehirns," *Deut. Zeit. f. Nerv.*, 1914, **50**, 96.
- [61] SHEBLOCK, E. B. "The Feeble-Minded," London Macmillan and Co., 1911.
- [62] STEINBISS, W. "Zur Kenntnis der Rhabdomyome des Herzens und ihrer Beziehungen zur tuberosen Hirnsklerose," *Vichow's Archiv*, 1928, **243**, 33.
- [63] VOGT, H. "Zur Pathologie und pathologischer Anatomie der verschiedenen Idiotieformen. II, Tuberosa Sklerose," *Monat. f. Psych. u. Neur.*, 1908, **24**, 106.
- [64] WEBER, F. PARKES and PERDRAU, J. R. "Periosteal neurofibromatosis, with a Short Consideration of the Whole Subject of Neurofibromatosis," *Quart. Journ. Med.*, 1930, **23**, 151.
- [65] WOLBACH, S. B., "Congenital Rhabdomyoma of the Heart," *Journ. Med. Res.*, 1907, **16**, 495.
- [66] YAKOVLEV, P. I., and GUTHRIE, R. R. "Congenital Ectodermosis (Neurocutaneous Syndromes) in Epileptic Patients," *Arch. Neur. Psych.*, 1931, **26**, 1145.
- [67] VON MEDUNA, L. "Tuberosa Sklerose und Gliom," *Zeit. f. d. g. Neur. u. Psych.*, 1930, **129**, 679.
- [68] SOARPATETTI. "Zwei Fälle frühzeitiger Erkrankung des Zentralnervensystem. (a) Multiple tuberosa Sklerose des Gehirns," *Arch. f. Psych.*, 1898, **30**, 537.
- [69] DORE, S. E. *Brit. Journ. Dermat.*, 1906, **18**, 215.

THE GRASP-REFLEX OF THE FOOT.

BY W. RUSSELL BRAIN AND R. DESMOND CURRAN.

It is only during recent years that the phenomenon known as the grasp-reflex of the hand has become familiar, and there is still much to be learned about both its physiological and its clinical significance. Our object in this paper is to draw attention to an allied reaction in the foot.

The reflex may justifiably be called a grasp-reflex, since in all respects it closely resembles a grasp-reflex of the hand, with which it is not uncommonly associated in the same individual. By calling it a grasp-reflex we avoid the introduction of a second flexor plantar reflex which might be confused with the normal flexor plantar response.

The foot grasp-reflex in infancy.—We were first led to study this reflex by the observation, which must have been made by many others, that, though in infancy a scratch upon the sole evokes an extensor plantar response, yet plantar flexion of the toes can readily and constantly be elicited by a different form of stimulus. We have studied this reflex in fifty children of various ages. The appropriate stimulus is light pressure upon the plantar surface of the distal part of the foot including the toes; the afferent focus appears to be the ball of the great toe. A light stroking movement from the heel forwards will also evoke it. The motor response, which is unilateral, is flexion and adduction of the toes. No constant associated movements have been observed, though inversion of the foot may occur at the same time. The reflex is tonic in character, since the new posture of flexion and adduction of the toes is often maintained for a quarter or half a minute or longer. If a thin pencil be used to elicit the reflex it may be grasped by the toes and held for a quarter of a minute or more. The flexed posture of the toes may persist during movements of flexion and extension at the knee and hip, if these should happen to occur. The reflex is not elicitable during sleep.

Age incidence.—The reflex has been sought in fifty children of various ages and without disease of the nervous system, and the results are tabulated below:—

GRASP REFLEX OF THE FOOT IN NORMAL INFANTS.

Number	Age	Present	Doubtful	Absent
24	Up to 9 months	24	—	—
28	Up to 1 year	26	1	1
9	One to 2 years	5	1	3
13	Over 2 years	1 (aged 3)	—	12

It will be seen that this reflex was elicitable in all children aged 9 months or less, and in almost all aged under a year, while it had disappeared in all but one child over the age of 2 years. This child, aged 3 years, suffered from rickets, and showed both the grasp-reflex and extensor plantar responses.

We found the foot grasp-reflex absent in two infants, aged 6 months, who both suffered from bilateral pyramidal lesions and exhibited marked spasticity. One was a hydrocephalic child and the other, whom we saw through the kindness of Dr. Kenneth Tallerman, suffered from a familial cerebral degeneration. It is impossible to say whether in such cases the foot grasp-reflex had never been acquired, or had been lost through destruction of the cerebral centres concerned, or was inhibited by the spasticity.

A recent investigation by Sittig [9] of the duration of the foot grasp-reflex in normal infants has yielded results similar to our own. Up to the age of 9 months the foot grasp-reflex was present in 136 and absent in 13 children. Up to the age of 1 year it was present in 157 and absent in 35.

Association with extensor plantar response.—The presence of the grasp-reflex of the foot thus corresponds roughly with the normal persistence of the extensor plantar reflex in infancy. As in all cases the response to scratching the sole was recorded, it is possible to determine how close this coincidence is. In 23 of the 50 children the grasp-reflex was associated with extensor plantar responses, in 11 cases with flexor responses. Of 16 individuals in whom the grasp-reflex was absent, 15 showed flexor plantar reflexes and only 1 extensor plantar reflexes. It is clear from these figures and from the ages of the children in the different groups, that the grasp-reflex tends to outlast the extensor plantar reflex. In only one instance did the reverse occur.

It may be of some interest to record our observations of the behaviour of the nociceptive plantar reflex at various ages. Up to the age of 6 months this was extensor in 17 out of 18, the exception being a child 6 months old. Between 6 and 9 months 2 children

showed flexor, and 2 extensor, reflexes. Between 9 months and a year 1 out of 4 gave extensor responses, and over 12 months, 2 out of 22. Although the change from extensor to flexor reflex usually occurs at the time at which the child is learning to walk, there is no constant correlation between these events, since the reflex may be flexor in children who have not walked, or extensor in those who have done so.

The foot grasp-reflex in mongolian imbeciles.—Having observed and investigated the grasp-reflex of the foot in infants, we sought to ascertain whether it could be found in later life as a result of pathological conditions, and observed that it was fairly common in mongolian imbeciles. We have investigated the reflex in 59 "mongols" ranging from 1 to 45 years of age. It was present in both feet in 23, and in one foot only in 5. It was absent in 20 and the result was doubtful, mainly owing to difficulties of examination, in 11. Thus the reflex was obtained from one or both feet in approximately half the cases. It is illuminating to arrange these results according to the ages of the patients:—

GRASP-REFLEX OF THE FOOT IN MONGOLIAN IMBECILES.

Age of Patient	Present	Absent	Doubtful
Under 5	3	—	—
5 to 10	9	2	2
11 to 20	18	6	7
21 to 30	1	9	2
31 to 40	1	2	—
41 to 50	1	1	—

Although the grasp-reflex was found in a mongol aged 45, it was rarely observed after the age of 20. Up to the age of 20 it was present in 25 out of 42 patients, after the age of 20 in only 3 out of 17. There are two possible explanations of this fact, either that a mongolian imbecile exhibits the reflex up to a greater age than the normal individual but ultimately loses it, or that it is present only in the lower-grade mongols who are not likely to live so long as those less severely affected.

The foot grasp-reflex in cases of localized cerebral lesions.—In 1926, Schuster and Pineas [7], in their paper on forced grasping, reported one patient who exhibited a grasp-reflex in the foot as well as in the hand. This was a girl, aged 19, who three years previously had had a febrile illness followed by left hemiparesis and hemiathetosis. After describing the grasp-reflex of the hand the authors continue: "Exactly analogous changes in the toes on the left side. On the lightest touch upon the

toes or the ball of the foot there followed a maximal flexion of all the toes. If it followed a touch with a lead pencil or similar object, this was strongly grasped until an intercurrent athetoid movement of the toes released it." Professor Schuster, in a personal communication, states that he has observed a grasp-reflex of the foot in one other patient besides the one just described.

Symonds [11], in 1928, at a meeting of the Neurological Section, showed a patient who exhibited right hemiparesis, together with optic atrophy following papilloedema. This patient had difficulty in relaxing the grasp of the right hand, and when she gripped the observer's fingertip under the toes of the right foot there was a persistent contraction, apparently of the long flexors of the toes, with flexion of the ankle. In both cases the prolonged grasp followed voluntary flexion, and Symonds reported the case as one of tonic innervation. In the discussion, however, Critchley [2] suggested the possibility of a grasp-reflex.

Sittig [10] has made a special study of the grasp-reflex both in the hand and in the foot. He has generously supplied us with notes of twenty-nine cases, most of them unpublished. In his twenty-nine cases he has found the reflex present in both hands and both feet three times, in one hand and the same foot once, in one hand alone five times, in both feet without the hands nine times, and in one foot alone eleven times. He has thus found the grasp-reflex present in the foot much more frequently than in the hand, viz., in twenty-four compared with nine patients. His cases were mostly intracranial tumours and vascular lesions. He concludes that "The grasp-reflex seems to occur also with other localization than the frontal lobe." As is the case with the hand grasp-reflex, Sittig has observed a patient in whom the onset of complete paralysis was followed by the disappearance of the grasp-reflex of the foot.

Freeman and Crosby [4], in a paper on the grasp-reflex, have reported three instances of its occurrence in the foot. All three were examples of cerebral arteriosclerosis. In one it was observed in both hands and both feet; in one, in both hands and one foot; and in the third, in one hand and one foot. Freeman [3] elsewhere likens the foot grasp-reflex in pathological states to the normal infantile reaction.

We have observed the foot grasp-reflex in the following four cases:—

(1) *Congenital choreo-athetosis*.—Ivy B., aged 2½. There was a long and difficult labour. The child was not noticed to be abnormal until it was 8 months old, when it was noticed that its right foot turned in when an attempt

was made to stand it on its feet. About the same time abnormal movements of the upper limbs were observed. At $2\frac{1}{2}$ years the child was clearly mentally defective; she was unable to speak and to sit up, and there were severe choreo-athetoid movements of the face and of all four limbs. She attempted to grasp with the hands objects presented to her, but the involuntary movements



FIG. 1.—Patient No. 1.—Foot-grasp reflex.

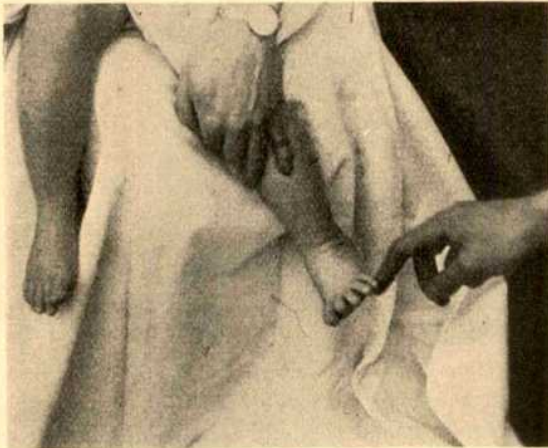


FIG. 2.—Patient No. 1.—Response evoked by scratching outer border of sole.
Compare with fig. 1.

rendered grasping extremely difficult. There was no grasp-reflex of the hands, but a vigorous grasp-reflex was readily elicitable in both feet. The slightest contact with the flexor surface of the toes or the distal half of the sole evoked strong flexion of all the toes, which were maintained in tonic flexion for quarter

to half minute or longer. If the reflex was evoked by bringing an object such as a pencil into contact with the plantar surface of the toes, this object was grasped by the toes and held for half a minute or more (fig. 1).

The tendon reflexes were brisk and equal; the right plantar reflex was flexor and the left extensor (fig. 2).

(2) *Unverified tumour of the corpus callosum*.—Mrs. H., aged 46. There was a seven years' history of "fainting feelings," which after three years developed into convulsions. Each convulsion was followed by a prolonged state of semistupor. There was no papilloedema, but there was bilateral weakness with some spasticity and extensor plantar responses. Radiography showed a rounded opaque area in the fronto-parietal region, slightly to the right of the middle line. This patient for a long period showed an extremely vigorous grasp-reflex in both hands, stronger on the right than the left, and at times forced groping was present on the right side. At the same time light stroking of the sole towards the toes elicited a prolonged flexion of all the toes, which was maintained as long as the observer's fingers remained in contact with the foot. This reflex was always more readily elicited in the right foot than in the left.

(3) *Subdural hæmatoma*.—John L., aged 57, farmer, a patient of Dr. W. A. Lister, of Plymouth, and Mr. Hugh Cairns, admitted to the London Hospital, August 24, 1931.

The patient enjoyed good health until May 24, 1931, when he suddenly complained of frontal headache. Subsequently headaches occurred occasionally until two weeks before admission, when they became more severe. Six days before admission became drowsy. Drowsiness varied markedly in intensity: at times he could be roused, at other times this was impossible. For four days he had been incontinent.

When examined on August 26 he was completely comatose. There was no papilloedema. He occasionally moved his limbs spontaneously and there was no evidence of paralysis of any limb. The tendon-jerks in the upper limbs and the knee-jerks were present but sluggish; the ankle-jerks and abdominal reflexes were absent. Both plantar reflexes were extensor, the right more definitely so than the left. Any moving stimulus applied to the right sole evoked a vigorous upward movement of the toe. The grasp-reflex was readily elicitable from both hands and both feet, being more vigorous in both instances on the right side. In the feet it was elicited by light pressure applied over the ball of the great toe or the flexor surface of the toes. Tonic flexion of the toes was well maintained and a pencil applied to the plantar surface of the toes was grasped and held for a number of seconds. Reflex grasping was better sustained in the right foot than in the left.

On August 28 ventriculography showed that both ventricles were displaced to the left, and there was a collection of air lying superficially to the cortex on the right side. Mr. Donald operated and carried out a right subtemporal decompression, and on opening the dura a large quantity of thin brown fluid, obviously old blood, shot out under pressure. The subdural hæmatoma was

evacuated, and although there was a temporary improvement with recovery of consciousness, the patient died on August 31 of bronchopneumonia. Post-mortem examination showed that the right hemisphere was still collapsed in the region previously occupied by the hæmatoma.

(4) *Meningioma of falx*.—A male, aged 50, was admitted to the London Hospital, under Dr. George Riddoch, with one year's history of headaches, attacks of unconsciousness and progressive dysphasia. Ten months before admission weakness of the right upper limb suddenly developed but subsequently improved, but weakness recurred seven weeks before admission. Vision had recently been deteriorating. On examination there were bilateral papilloedema and right hemiparesis and hemiapraxia, with marked verbal dysphasia. A strong grasp-reflex was present in the right hand and also in the right foot. In the latter a scratch on the sole yielded an extensor plantar response, but a light stroking movement with the fingers along the sole from the middle towards the toes evoked strong tonic flexion of the toes. The response also occurred if the observer brought his finger-tips into contact with the plantar surface of the toes. The toes then became flexed and grasped the tips of the fingers, and this tonic flexion was so powerful that the leg could be lifted off the bed. A pencil presented to the plantar surface of the toes was similarly grasped and held.

Mr. Hugh Cairns operated on this patient and removed a meningioma weighing 55 grm. The tumour was embedded in the medial aspect of the left frontal lobe, reaching back to within about 2 cm. of the precentral gyrus. It was about 6 cm. in antero-posterior and 4.5 cm. in other diameters. It was lightly attached to the left side of the falx, just below the superior longitudinal sinus, over a small area 1 to 2 cm. in diameter.

After operation the grasp-reflex of the hand disappeared within forty-eight hours. That of the foot was not investigated for ten days, when it also was absent. There was a rapid improvement in all the other symptoms.

PHYSIOLOGICAL AND ANATOMICAL CONSIDERATIONS.

The foot grasp-reflex must be distinguished from the normal flexor plantar reflex. When, as in the young infant, the slightest nociceptive stimulus to the sole evokes an extensor plantar response, the normal flexor reflex can easily be excluded because it cannot be obtained. When, however, this can be elicited in an adult patient the distinction requires care. The normal flexor reflex, however, cannot in our experience be elicited by mere contact or light pressure without a moving stimulus; and in the grasp-reflex the motor response is confined to the flexors and adductors of the toes and is tonic and not phasic in character. It must also be distinguished from Rossolimo's reflex in which sudden flexion of the toes is elicited by a tap upon the ball of the foot. This reflex is a contraction of the long flexors of the toes, probably evoked

by suddenly stretching them. The grasp-reflex is obtained without displacement of the foot at any joint. Freeman and Crosby's account of their method of eliciting the reflex suggests that in two of their cases they may have obtained Rossolimo's reflex rather than the grasp-reflex.

The grasp-reflex of the foot is distinguished from the extensor thrust by its tonic character, and the fact that the motor response is confined to the flexors and adductors of the toes. When, as often happens in the infant, the foot is in a posture of dorsiflexion before the reflex is elicited, plantar flexion of the foot plays no part in the response. For similar reasons we can distinguish it from the positive supporting reaction of Magnus, and the "Widerstandsbereitschaft" of Mayer and Reisch [5]. The evidence points, in fact, to its being a specific reflex.

Like the hand grasp-reflex, it is usually associated with a lesion involving the frontal lobes, and there are indications that with a lesion near the leg areas, for example a tumour of the falx, the foot grasp-reflex may be present in the absence of the hand grasp-reflex. As in the case of the latter, it has been described with lesions in other situations, but even so both should probably be regarded as evidence of disturbance of function of the prefrontal region.

The similarity of the foot grasp-reflex to the hand grasp-reflex and their association in the same patient naturally leads us to look for a similar interpretation of both. Adie and Critchley [1] drew attention to the resemblance between the pathological hand grasp-reflex and the normal character of reflex and spontaneous grasping in infancy. A similar analogy holds good of the foot grasp-reflex which can also be studied in any infant.

These reflexes appear to be elicitable only when there is a deficit of certain paths which originate in the frontal lobes and which may be normally undeveloped as in the infant, abnormally undeveloped as in the mongolian imbecile, or destroyed by disease. The precise course of these paths has recently been investigated in the case of the hand grasp-reflex by Schuster and Casper [8]. They report the pathological findings in a number of cases, in three of which the brains were cut in serial sections. They conclude that the hand grasp-reflex is a release phenomenon, and is normally inhibited by impulses which originate in the first frontal convolution and the gyrus fornicatus and are brought to bear upon the origins of the pyramidal tract in the precentral convolution. Each pyramidal tract is believed to be in this respect under the control of both frontal lobes, the inhibitory fibres from the opposite

hemisphere crossing in the corpus callosum to join those from the ipsilateral hemisphere. In order that the grasp-reflex may appear it is necessary that the fibres from both frontal lobes shall be interrupted. The lesion in most cases is so situated as to involve the first frontal convolution on one side and the adjacent half of the corpus callosum, thereby interrupting the fibres from the opposite side.

The commonest lesions which are appropriately situated to allow reflex grasping to occur are intracerebral tumours involving the medial aspect of the frontal lobe, tumours of the corpus callosum and of the falx, and cerebral softening due to thrombosis of branches of the anterior cerebral artery. Diffuse cerebral degeneration involving the frontal lobes may produce the same effect. The occurrence of bilateral hand and foot grasp reflexes in our third patient who had a subdural hæmatoma in the right fronto-parietal region cannot be explained as a result of direct pressure by the hæmatoma upon the medial aspect of the frontal lobes, but was probably due to transmitted pressure, the displacement of both hemispheres, clearly indicated in the ventriculogram, causing these areas to be compressed against the falx.

These anatomical considerations, however, do not afford an explanation of the nature of the grasp-reflex, nor do they explain why the human infant exhibits reflex prehension with its toes. Prehensile toes naturally suggest the anthropoid apes and monkeys, and we therefore studied the palmar and plantar reflexes of such of these animals as were accessible at the Zoological Society's Gardens, facilities being kindly given us by Dr. Vevers and the head keeper of the monkey house. We examined one chimpanzee, one orang-outan, six monkeys and one lemur. Only one showed a hand grasp-reflex, a young pig-tailed monkey, 12 months old. All the monkeys showed well-marked grasping in the feet in response to moving contact, but this was not evoked by simple contact or by pressure. Neither of the anthropoid apes showed a grasp-reflex in the feet. The prehensive functions of the adult monkey's foot are activities of a highly specialized character. The grasp-reflex in man seems simpler and more rudimentary, an activity of a lower order. The infant monkey, however, exhibits true reflex grasping. As soon as it is born it is slung beneath the mother's belly, clinging to her flanks with its hands and feet and receiving no support whatever from her. Though only a day or two old, it holds on while she jumps from bough to bough, and does not leave her until it is weaned. We have observed a number of infant monkeys, some within a few days of birth, and the tenacity of their grasp of the mother is astonishing.

Richter [6] has recently investigated the hand grasp-reflex of the infant monkey. He found that it was much stronger than in the newborn human infant, one of the monkeys hanging for over thirty-three minutes by one hand alone. The reflex hand and foot grasps of the infant monkey offer a phylogenetic explanation of reflex grasping.

The foot grasp-reflex of the mongolian imbecile should not be regarded as indicating that the mongol is in any peculiar sense simian. Anatomical evidence strongly suggests that mongolism is due to a check in development during the third month in foetal life, and that the characteristic mongolian traits are foetal rather than simian. At least they are simian only in the very general sense that the human foetus in its development to some extent recapitulates human evolution. It is not surprising that the mongol should therefore exhibit a reflex characteristic of early human infancy.

SUMMARY.

(1) A grasp-reflex of the foot similar to that of the hand is described.

(2) The foot grasp-reflex is normally present in the human infant during the first year of life, and usually persists somewhat longer than the extensor plantar reflex.

(3) The foot grasp-reflex is elicitable in approximately 50 per cent. of mongolian imbeciles.

(4) It may also occur as a result of lesions of the frontal lobe.

(5) A homologous foot grasp-reflex is present in the infant monkey.

We are indebted to Dr. George Riddoch and Mr. Hugh Cairns for kindly allowing us to investigate their cases, and to Dr. S. Behrman for the photographs illustrating Case 1.

REFERENCES.

- [1] ADIE, W. J., and CRITCHLEY, M. *Brain*, 1927, **50**, 142.
- [2] CRITCHLEY, M. *Ibid.*, 1928, **51**, 128.
- [3] FREEMAN, W. "Human Biology," 1929, **1**, 416.
- [4] FREEMAN, W., and CROSBY, P. T. *Journ. Amer. Med. Assoc.*, 1929, **93**, 7.
- [5] MAYER, C., and REISCH, O. *Deutschs. Zeitschr. f. Nervenheilk.*, 1928, **102**, 28.
- [6] RICHTER, O. P. *Arch. Neurol. and Psychiat.*, 1931, **26**, 784.
- [7] SCHUSTER, P., and PINEAS, H. *Deutsch. Zeitschr. f. Nervenheilk.*, 1926, **91**, 29.
- [8] SCHUSTER, P., and CASPER, J. *Zeitschr. f. d. ges. Neurol.*, 1930, **129**, 739.
- [9] SITTING, O. *Medizinische Klinik*, 1932, **28**, 934.
- [10] *Idem.* Personal communication.
- [11] SYMONDS, C. P. *Brain*, 1928, **51**, 121.

GLOSSOPHARYNGEAL NEURALGIA.¹

BY W. S. KEITH.

As late as 1926 it was said by Dana of the glossopharyngeal nerve, "It has no tic or palsy or algia . . . it receives only disregard and aloofness from surgeons and clinicians." This statement appears in a discussion of glossopharyngeal neuralgia by Stookey, and is reproduced here to emphasize how recently this condition was described.

The earliest reports of glossopharyngeal neuralgia have been fully discussed by Dandy, Stookey and others. Weisenberg, in 1910, was the first to describe the symptoms of irritation of the glossopharyngeal nerve, in a case of tumour of the cerebellopontine angle. In 1920, Sicard and Robineau reported three cases each of which was probably true glossopharyngeal neuralgia. In 1921, Harris described "a rare form of paroxysmal neuralgia or tic douloureux which affects the glossopharyngeal nerve." Since this time reports of this disease by Doyle, Adson, Harris, Albright, Singleton, Goodyear, Dandy, Stookey, Fonio, Hansel, Bailey, Brock and Martin have appeared. Dandy collected and published in tabular form detailed information in twenty cases. Seventeen additional cases are here recorded in tabular form and three of these are reported in detail.

Case 15.—Mrs. W. J. B. Aged 44. In 1911 while eating some fruit this patient was suddenly seized with a sharp pain in the left side of her throat. She thought she had taken a piece of glass into her mouth. In 1912 she had her left tonsil removed with complete relief from pain for three years. Between 1915 and 1922 she had about six painful attacks lasting up to three or four months each. The pain was at its worst in early spring but disappeared in summer. Sweet things such as honey, syrup or fruit, and sour things such as tomatoes, pickles or vinegar, always brought on an attack. She was unable to take solids or cold liquids when most subject to pain and at these times, chewing, speaking or even stooping over might initiate an attack. When subject to attacks she would remain in bed and would refuse all nourishment. She salivated freely and would let the saliva run out of her mouth from fear of swallowing it. The attack itself came suddenly, but sometimes there were one or two warning throbs. The sensation was described as being like a knife

¹ From the Neuro-surgical Service of the Toronto General Hospital.

Case number	Author and year	Age and sex	Duration of pain	Nature of pain	Location and radiation of pain	What induces pain	Duration of paroxysms	Pain in ear
1	Singleton 1926	F. 45	2 years	Intense suffering	Left side of throat radiating to side of neck and to ear	Swallowing or talking	..	+
2	Singleton 1926	F. 46	Several years	Severe paroxysmal pain	Posterior part of tongue, tonsillar region, deep in neck below the angle of jaw	..	..	..
3	Albright. 1926	F. 66	Few months	Severe spasmodic	Began in throat and radiated to and was worst in ear. Later around ear and over side of face. Was in teeth too	Swallowing, taking a breath, talking	Moment or two	+
4	Hansel .. 1928	F. 28	2 years	Excruciating and lancinating	Left side of pharynx radiating to ear	Swallowing, chewing, talking	Few seconds	+
5	Hansel .. 1928	F. 47	5 years	Paroxysms of excruciating pain	Right side of pharynx radiating to ear	Eating and talking	30 to 60 seconds	+
6	Hansel .. 1928	F. 61	18 months	Severe lancinating pains	Right side of throat radiating to ear	Chewing, swallowing, drinking cold water	Few seconds	+
7	Hansel .. 1928	M. 52	10 years	Excruciating and lancinating pain	Left side of throat and neck radiating to ear	Talking, chewing, swallowing	80 seconds	+
8	Hansel .. 1928	M. 60	2 years	Stabbing, excruciating pain	Left side of pharynx radiating to ear (tragus)	Talking, swallowing, chewing	Few seconds	+
9	Fonio .. 1928	M. 75	..	Very intense pain	Right tonsil and right side of throat radiating to ear and towards eye	Speaking, chewing, swallowing	Several seconds	+
10	Stokey .. 1928	M.	..	Very frequent and severe attacks of pain	..	..	..	..
11	Brock .. 1931	M. 61	Few months	Severe paroxysms	Right side of tongue and tonsil and radiating to ear	Swallowing or protrusion of tongue	Transient	+
12	Bailey .. 1931	F. 59	6 months	Boring pain	Left tonsil and left side of throat radiating to ear	Swallowing	..	+
13	Bailey .. 1931	F. 86	6 years	Sudden excruciating pain	Base of tongue and left side radiating to ear	Swallowing	Transitory	+
14	Martin .. 1931	M. 61	8 years	Severe stabbing and burning	Pain began in ear and radiated to throat. Pain most severe in ear	Swallowing or talking sometimes	Few seconds	+
15	Keith .. 1932	F. 44	12 years	Stabbing and twisting	Side of throat and tonsillar area. Later radiating deep in ear and neck	Swallowing, especially sweets or sour things	Less than 30 seconds	+
16	Keith .. 1932	M. 45	8 years	Agonizing sudden pain	Side of throat and jaw	Swallowing, drinking	20 seconds	+
17	Keith .. 1932	F. 60	14 years	Boring pain	Deep in ear and behind and in lobule—radiating somewhat to throat	Swallowing	$\frac{1}{2}$ to 3 minutes	+

Pain uni-lateral	Periods of remission from pain	Trigger zone	Any associated disease	Treatment	General remarks
+	+	..	None found	Avulsion of glossopharyngeal nerve in the neck	During attack a finger pressed over ear. The other hand pressed against side of neck
+	+	..	..	Alcohol injection of Gasserian ganglion with total anaesthesia. No relief	Later in another Clinic the root of the 5th nerve was divided. No relief. Post-operative diagnosis. Glossopharyngeal neuralgia
+	+	+	None found	Alcohol injection of Gasserian ganglion without relief. Advised operation on glossopharyngeal nerve	Greatest severity of pain was "right in the ear." Cocaine anaesthesia of right tonsillar region temporarily stopped the spasms
+	+	..	None found	Wisdom teeth removed	..
+	+	..	None found	Nil	..
+	+	..	None found	Refused operation	..
+	+	..	None found	Operative treatment advised	Had had operation for lung abscess and had diabetes
+	+	..	None found	Patient did not wish operative treatment	..
+	+	..	Aneurysm of common carotid artery	Three operations on aneurysm. Then avulsion of glossopharyngeal nerve in neck	..
..	..	..	..	Intracranial section of glossopharyngeal nerve	Feeling of dryness of the mouth on the same side as the pain
+	..	Side of base of tongue	None found	Novocain and alcohol injection three times. 9 months-1 year apart. Relief each time	Had abscess in right pyriform fossa three years before. Died. No autopsy
+	..	..	Carcinoma of the larynx	Intracranial section of glossopharyngeal nerve by Dr. Davenport	Complete relief from operation. Pain later appeared on the other side and patient died two months after operation
+	..	..	None found	Intracranial section of glossopharyngeal nerve	Removal of teeth and injection of alcohol into mandibular nerve gave no relief
+	+	..	None found	Phenazone and gelsemium	Left side of throat felt dry. Increased flow of saliva with spasms
+	+	..	None found	Avulsion of glossopharyngeal nerve in neck and division of pharyngeal branch of vagus	Has had severe pain at times since operation
+	+	Between tonsil and tongue	None found	Avulsion of glossopharyngeal nerve in the neck	Cocaine anaesthesia of left tonsillar region temporarily stopped the spasms
+	+	..	None found	Avulsion of glossopharyngeal nerve in the neck	..

stabbed into and twisted in the side of the throat. She stated that the worst spasms forced her to her knees so that she prayed she might die before another attack came. The pain never lasted longer than half a minute. It seemed to be inside the throat in the region of the root of the tongue on the left side and just below the angle of the jaw deep in the left side of the neck. In the last two or three periods of attacks the pain had often radiated deep into the left ear.

On physical examination the patient was found to have a colloid goitre of moderate size. No other abnormalities were found. X-rays of the teeth were reported normal. A diagnosis of glossopharyngeal neuralgia was made.

Operation.—March 21, 1923. Under intra-tracheal ether anæsthesia an incision was made below the left mandible. The glossopharyngeal nerve was exposed and divided and the proximal end was avulsed. The pharyngeal branch of the vagus nerve was divided. On March 22 the pain was gone. On April 2 the patient was discharged completely relieved of symptoms. In December, 1924, the same pain returned. One series of spasms at this time was the worst she had ever experienced. In the springs of 1925, 1927 and 1929, she had similar attacks lasting over periods of from one to three months. With the exception of the severe bout mentioned above, the pains since operation have been less severe than those before.

Case 16.—Mr. W. H. E. Aged 45. In March, 1923, the patient awoke one night with pain in the left side of his throat. It disappeared before morning. In March, 1924, while drinking cold water he was suddenly seized by a terrific pain in the left side of his jaw and throat. He stated that it felt as if he had been hit by a base-ball bat on the angle of his jaw. There were no more attacks until October, 1925, when a more severe agonizing pain occurred in the same place very suddenly while drinking cold water. From this time he suffered frequently from pains of varying severity until he presented himself for examination in January, 1926. There were intervals of as long as a month between major attacks. These attacks came without any warning, sometimes while reading but usually while talking, eating or drinking. Sneezing or coughing did not bring them on. They lasted about twenty seconds and were so severe that he had great difficulty in localizing them. However, as each pain passed off the region of the left tonsil and back of the tongue on the left side remained sore. He also noted that during the severe attacks he had pain immediately in front of the external auditory meatus. This latter pain seemed to radiate toward the temporal region. He complained of two types of pain between the major attacks. One was described as of an oat husk caught between his left tonsil and tongue and from here small, shooting and quick pains radiated. They kept him in fear of the so-called big pain. The other unpleasant sensation was a dull ache as if a very heavy weight were suspended from the affected parts. The patient seemed to be most subject to pain in the spring and autumn. He had small pains only in the hot weather. In January, 1926, he stated that there was pain in the two left posterior lower teeth with some insignificant radiation to the upper lip and eyelid. He once got relief by having the painful area swabbed with cocaine.

On examination it was observed that there was a "trigger" spot between the left tonsil and the tongue, indeed, the patient dropped to the floor with severe pain when touched on this spot. When asked to cover the painful area however, he placed his hand over the whole of the left mandible. At this time a note was made that the condition was probably not glossopharyngeal neuralgia. General physical examination was entirely negative. A diagnosis of neuralgia of the third division of the trigeminal nerve was made.

On January 16, 1926, alcohol injection of the left mandibular nerve was done. On March 8, there was no anæsthesia in the mandibular area, but the injection had given relief. The patient dreaded the return of pain at a time when it would be almost impossible for him to come for operation, so partial division of the sensory root of the fifth nerve was advised.

Operation.—March 22, 1926. Under intratracheal ether, the usual approach through the middle fossa to the Gasserian ganglion was carried out. About two-thirds of the sensory fibres were avulsed. The motor root was left intact. On April 5, 1926, he returned to his home. He had been free from pain since the alcohol injection. In January, 1928, the patient returned because of stabs of pain in the original spot. There was complete loss of sensation in the whole left trigeminal area.

On February 13, 1928, the following note was made: For three or four days the patient has been lying in bed, refusing to swallow anything. Some food became lodged between his tonsil and tongue and nearly sent him crazy. The pain starts in the tongue and anterior pillar of the tonsil and goes down just below the angle of the jaw and up just in front of the ear. Spasms last about twenty seconds. A diagnosis of glossopharyngeal neuralgia was made.

Operation.—February 14, 1928. The glossopharyngeal nerve was exposed through an incision below and behind the mandible. It was avulsed from above and below. About two and one-half inches of the nerve were removed. Four hours after operation it was impossible to produce the old pain by any form of stimulation. In February, 1929, it was noted that the palate elevated in the midline. There was no pain, but there was anæsthesia in the posterior part of the tongue on the left side and around the left tonsil.

The patient reported that during the winter of 1929-1930, he had several jerking feelings without pain, in the left side of his face and head. In October, 1930, small pains radiating from the "oat husk" area into his throat and tonsil region began again and caused him concern all winter. He stated that he would rather die than have the severe attack again.

Case 17.—Mrs. C. K. Aged 60. In 1916, for four or five days the patient had her first attacks of pain in the region of the right ear. In 1917, and in 1922, respectively, the pains recurred for from four to six weeks each time. The pain was referred to the external auditory canal, the lower one-third of the pinna and the area immediately behind the head of the mandible. It was brought on chiefly by drinking cold liquids, but swallowing was sufficient to induce an attack at the worst times. The severe pain lasted one to three minutes, but a burning sensation lingered for some five to ten minutes.

Beginning about September, 1930, the patient had occasional slight "warning" pain in the same place. In January, 1931, she caught a cold and while she was recovering in February the pains returned worse than ever. A severe spasm was described as follows: For about three minutes or more she had a sensation as if an auger were being bored into her right ear. The boring then stopped and a red-hot rod was left in the hole for five to ten minutes. The spasms were brought on by swallowing. She stated that for as long as ten days at a time she had been unable to swallow anything but small amounts of warm fluids. Yawning, sneezing and coughing also induced spasms. During the attacks there was some pain in an indefinite area in the region of the right tonsil, but this was apparently insignificant in comparison with the more superficial pain. In May, 1931, she had a nerve in the right side of her face injected through her nose with some temporary relief. Two weeks later some bone was removed from inside her nose and another injection was done. The injection was repeated a fortnight later.

On examination, the patient was thin and appeared to be about 65 years old. The blood-pressure was 190/90. When asked where her pain was located, she pointed to the region between the head of the mandible and the mastoid, and very gingerly grasped the pinna behind and below the external auditory meatus. She would not allow the region of the right ear to be touched, because the least manipulation would bring on a spasm. No "trigger" spot could be found inside her mouth. Gagging always induced a spasm. The spasms were not as bad as they had been, and lasted not more than one-half to one minute. During the attack she cried and moaned, but did not touch the painful area. Her head was held turned slightly to the left, and she resented movement in any direction. Movements were very slow and deliberate. Digital pressure or pinching of the skin anywhere within two inches of the external auditory canal produced a spasm. Even pressure on the clavicular tendon of the sternocleidomastoid muscle caused severe pain. There was some hypæsthesia in the region of the second division of the right trigeminal nerve. There were no other neurological findings.

A provisional diagnosis of glossopharyngeal neuralgia was made, though it was felt that some of the fibres of the vagus might be involved as well.

Operation.—July 10, 1931. Incision was made below the ramus of the right mandible. The glossopharyngeal nerve was exposed and divided. The proximal end was avulsed, about one and one-half inches of the nerve being removed. The distal end was buried in the digastric muscle. Four hours later one could manipulate the pinna and neighbouring parts and produce only pain referred to the incised wound.

On July 20, 1931, the patient was able to eat, drink, talk, sneeze and cough as she pleased, and without pain. There was no tactile sensation on the front of the soft palate on the right side. There was absence of taste for sugar and salt on the posterior one-third of the right side of the tongue. The palate was elevated in the midline, but it seemed to hang a little lower on the right side than on the left. There was no disturbance of tactile sensation in the region of the right ear.

The term *tic douloureux* has for a long time been synonymous with a certain type of neuralgia of the trigeminal nerve. In view of the marked similarity between cases of glossopharyngeal neuralgia and the much more common trigeminal variety, and indeed their not infrequent confusion, it seems reasonable to use *tic douloureux* as a generic term to include both conditions.

The diagnosis of *tic douloureux* rests upon the history of the disease and observation of the attacks. Abnormal physical findings are almost always absent. It follows, therefore, that the two anatomical types of *tic douloureux* must be distinguished by analysis of the history. Observation of the attacks may be an aid in some cases. For these reasons it is justifiable to consider in some detail all the reports of glossopharyngeal neuralgia.

Tic douloureux of the glossopharyngeal nerve usually occurs after 40 years of age. The paroxysms of pain are always very severe and of brief duration. Dandy suggests that the pain is usually more severe and of shorter duration than in trigeminal neuralgia. The pain in practically every case is induced by swallowing or some form of movement of the fauces, pharynx or tongue, although it may occur spontaneously as well. In every case the pain is unilateral except where an associated neoplasm has crossed to the other side. In this latter instance the character of the pain is likely to have changed. It is probable that in every case unassociated with a neoplasm there have been one or more periods of spontaneous remission from pain. This observation, however, is not mentioned in all case reports. One remission of eight years in Case 17 is the longest on record. The pain nearly always begins in the throat, in the region of the tonsil, or in the base of the tongue. The place of origin of the pain is nearly always the seat of its greatest severity. In most cases the pain begins and is most severe in the throat. In Cases 14 and 17 the pain began in the ear and was most severe in the ear. In Case 3 the pain began in the throat but was most severe in the ear.

Radiation of pain to the ear at some stage in the disease nearly always occurs. It is usually described as being deep in the ear. The anatomical explanation of this pain deep in the ear lies in the fact that the glossopharyngeal nerve contributes a branch called Jacobsen's nerve to the tympanic plexus. Dandy makes the statement that there is no external sensory supply by the glossopharyngeal nerve. However Ramsay Hunt collected anatomical, embryological and experimental evidence which shows that the glossopharyngeal nerve through a small

twig to the auricular branch of the vagus nerve contributes to the supply of the posterior part of the tympanum, the posterior wall of the auditory canal, part of the concha and a strip on the postero-medial surface of the auricle, and the immediately adjacent mastoid region. Entirely new evidence of the superficial distribution of glossopharyngeal fibres in this area is to be found in the fact that this was the exact distribution of pain in Case 17, and that part of this area was the chief seat of superficial pain in Case 14. In Case 10 no sensory loss could be demonstrated in this area after intracranial section of the glossopharyngeal nerve. This is due to the fact that this small area is completely overlapped by other nerves of the region. Additional evidence of the contribution of the 7th, 9th, and 10th cranial nerves to the supply of this superficial area is to be found in Ramsay Hunt's observations on herpes zoster of these nerves and in an interesting case reported by Neve; this patient had herpes zoster of the left half of the soft palate with pain behind and below the left ear and down the left side of the neck. He considered this to be a case of herpes zoster of the glossopharyngeal nerve.

In a few cases the pain seems to overflow the area supplied by the glossopharyngeal nerve and spread down over the upper cervical segments or up into the trigeminal region. It would appear that this usually occurs late in the history. In Cases 1 and 17 there was some pain down the side of the neck. In Cases 3, 9 and 16 the pain radiated somewhat into the trigeminal area, into either temporal or mandibular regions. Occasionally the teeth are complained of. In Case 16 the patient had some pain in his back lower teeth, and in one of Dandy's cases the patient felt as if his teeth "would jump out of their sockets."

Two factors contribute to the patient's difficulties in describing the pain. In the first place, whereas the glossopharyngeal nerve is almost entirely distributed to deep structures, there may be an unconscious tendency for some patients to interpret their pain in terms of superficial structures. In the second place, the pain is often so severe that the patient has difficulty in localizing it. It is probable that both these factors were present in Case 16.

In Cases 10, 13 and 14 there was a sensation of dryness in the painful side of the throat. In the latter case there was also increased flow of saliva in the paroxysms. In some instances increased salivation may be more apparent than real, owing to accumulation of saliva through fear of swallowing. "Trigger" spots and marked tenderness, or rather perhaps fear of touching the part, seem to be different degrees of the

same thing, and are well marked only when the patient is most subject to attacks. The seat of the worst pain is usually that of the "trigger" spot. In one of Dandy's cases the patient found that he could swallow with impunity for a few moments following a paroxysm. As in trigeminal neuralgia, patients sometimes adopt certain attitudes or movements during the paroxysms. These include placing tip of index finger in the auditory canal and wiggling it around, one finger pressed to the ear and the other hand to the neck, grasping the table, leaning forward to let saliva run from the mouth, &c.

Of thirty-seven cases of glossopharyngeal neuralgia reported, two had carcinoma of the tonsil, one had carcinoma of the larynx, one had an aneurism of the internal carotid artery, and one had a tumour of the cerebello-pontine angle. The incidence of associated disease, therefore, is much higher than in trigeminal neuralgia, and this fact should always be remembered when the diagnosis of glossopharyngeal neuralgia is made.

Treatment—It has long been established that section of a sensory root proximal to its ganglion results in permanent loss of sensation in the region supplied by the nerve. This is the only attack on the nerve which assures that the loss will be permanent. Intracranial section of the glossopharyngeal nerve, as advocated by Adson and carried out by Davenport (Case 12), Dandy and Stookey, is, then, the only sure method of permanently relieving the patient's pain. A case recorded by Adson and No. 15 of this series are known to have had recurrence of pain following avulsion of the nerve in the neck. Indeed, it was this former case which prompted Adson to work out his intracranial operation. It seems certain that Stookey's prediction that section of the dorsal root will prove the only successful procedure for glossopharyngeal neuralgia will be vindicated. Avulsion of the nerve in the neck may occasionally be indicated when the operative risk is great or where the diagnosis is in doubt. There seems to be a general agreement that there is almost no subjective disturbance in the throat following either operation. There must be a very few instances, such as Case 14, in which glossopharyngeal neuralgia is so much relieved by drugs that operative interference is unwarranted.

According to Dr. K. G. McKenzie, however, it is questionable if intracranial section of the nerve has sufficient advantage over extracranial section to justify what is undoubtedly a more formidable procedure. Extracranial avulsion of the nerve immediately stops the pain of a true glossopharyngeal neuralgia. The operation is an easy one as it is a

simple matter to palpate the styloid process, and from this landmark dissect out the stylopharyngeus muscle and locate the glossopharyngeal nerve in its characteristic relationship to the muscle. He believes it is unlikely that regeneration of the nerve will take place if the distal part of the nerve is sutured into fascia or muscle with silk, as in Case 17.

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REFERENCES.

- ADSON, A. W. *Arch. Neurol. and Psychiat.*, 1924, **12**, 487.
ALBRIGHT, G. O. *Laryngoscope*, 1926, **36**, 407.
BAILEY, P. *Surg. Clin. North America*, 1931, **11**, 61.
BROCK, S. *Laryngoscope*, 1931, **41**, 48.
DANA, O. L. *Arch. Neurol. and Psychiat.*, 1926, **15**, 675.
DANDY, W. E. *Arch. of Surg.*, 1927, **15**, 198.
DOYLE, J. B. *Arch. Neurol. and Psychiat.*, 1929, **9**, 34.
FONIO, A. *Deut. Zeit. f. Chir.*, 1928, **207**, 325.
GOODYEAR, H. M. *Arch. of Otolaryngology*, 1927, **5**, 341.
HARRIS, W. *Brit. Med. Journ.*, 1921, **2**, 896.
Idem. "Neuritis and Neuralgia," London, 1926.
HANSEL, F. K. *Ann. Otol., Rhin. and Laryng.*, 1928, **37**, 440.
HUNT, J. R. *Arch. Int. Med.*, 1910, **5**, 631.
MARTIN, J. P. *Brit. Med. Journ.*, 1931, **1**, 533.
NEVE, G. T. *Ibid.*, 1919, **2**, 630.
SINGLETON, A. O. *Ann. Surg.*, 1926, **83**, 888.
STOCKEY, B. *Arch. Neurol. and Psychiat.*, 1928, **20**, 702.

SYPHILITIC HYDROCEPHALUS IN THE ADULT.

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FROM the frequency with which the basal meninges are affected in the secondary and tertiary stages of syphilis one might expect that syphilitic hydrocephalus would be common; and undoubtedly the milder forms of hydrocephalus in infants are often due to syphilis. Thus Jeans and Cooke found hydrocephalus in one-third of the syphilitic children in their clinic in whom the nervous system was in any way affected. The hydrocephalus was always of the communicating type and was never extreme. Ibrahim is of the same opinion; in his own experience the greater degrees of hydrocephalus are practically never due to syphilis, but he found occasional references in the literature to syphilitic cases of non-communicating hydrocephalus in which the heads were very large. On syphilitic hydrocephalus in the adult, however, the literature is strangely silent. Most textbooks make no reference to it; even Jakob, who devoted more than 250 pages to the pathology of cerebral syphilis and described gummatous meningitis with a wealth of detail, does not mention it. Gowers, Oppenheim and Nonne are equally silent, although Oppenheim's description of the symptomatology of basal gummatous meningitis resembles very closely that found in our hydrocephalic cases. Collier and Adie, in Price's "Textbook of the Practice of Medicine," seem to be the only authors who draw attention to acquired syphilis as a cause of hydrocephalus. They mention three post-mortem cases, in which however there was "no obstructive lesion by which ventricular distension could have arisen mechanically." It would therefore appear to be a rare cause of death.

We have attempted to estimate its incidence by an examination of the post-mortem records at the National Hospital, Queen Square. During the past twelve years, among 997 autopsies at this hospital, there were twelve cases of hydrocephalus. Of these two were congenital and in two the condition followed meningococcal meningitis. In three the ætiology was doubtful; two may have been syphilitic as there was considerable arachnoiditis, but beyond this there was no definite

evidence. In five the evidence of syphilis was considered sufficient to warrant their inclusion in this paper. In two of these the immediate cause of death was a decompressive operation undertaken to save the patient's eyesight. In addition two patients who had been under treatment for basal gummatous meningitis in the hospital died suddenly at home, and were the subjects of inquests from which we were fortunately able to collect pathological material. Thus death was directly due to hydrocephalus in five of our cases.

During the same period the post-mortem records include six cases of syphilitic vascular disease, three of other forms of cerebral syphilis, and thirty-two cases of general paralysis. If these figures were trustworthy, syphilitic hydrocephalus in the adult would appear to rank along with syphilitic vascular disease as a cause of death, but the figures are invalidated by the fact that cases of cerebral hæmorrhage of syphilitic origin are usually either admitted to general hospitals or die at home, whereas cases of more subacute onset and obscure nature, especially those associated with papilloedema or blindness, would be sent to a special hospital for nervous diseases.

There appears to be no doubt, however, that syphilitic hydrocephalus is definitely more common at the present day than the form of gummatous meningitis associated with the presence of isolated large gummata. Of this condition no fatal case is found in the records of the past twelve years, and only two cases were subjected to operative treatment during that period. On the other hand if we refer to such neurological classics of the pre-Wassermann era as Gower's Manual and the earlier editions of Oppenheim's textbook we gain the impression that isolated gummata "varying in size from that of a nut to that of a walnut" (Gowers) are among the commoner lesions of cerebral syphilis. Oppenheim it is true emphasizes the frequency with which gummatous meningitis assumes a more diffuse form, but in his experience also large gummata were not uncommon.

The post-mortem records at the National Hospital for the years 1893 to 1914 inclusive contain ten cases of cerebral gumma. In one of these the chief lesion and the direct cause of death was hydrocephalus of the non-communicating type associated with numerous meningeal gummata the size of peas. This was the only fatal case of syphilitic hydrocephalus during this period. It is probable, however, that the milder forms of hydrocephalus, especially those of the communicating type, are not uncommon, but are more amenable to treatment; and the symptoms produced by distension of the ventricles and increased intra-

cranial pressure are often attributed, as by Oppenheim, to diffuse involvement of the meninges. This supposition is confirmed by the descriptions, in the older literature on acquired hydrocephalus, of lesions such as chronic meningitis and granular ependymitis which suggest a syphilitic ætiology.

It seems, therefore, that syphilitic hydrocephalus in the adult is not so rare as to be unimportant, and our experience indicates that, especially in the more acute cases of the non-communicating type, there is still a risk of mistaken diagnosis and faulty treatment. A record of seven cases in which post-mortem evidence is available may, therefore, be of value both in giving an indication of the symptomatology of the condition and in establishing its pathological basis.

SUMMARY OF CASE 1.

A woman of 39 presented the symptoms and signs of increased intracranial pressure. She also had minor, and later, major epileptiform seizures, during one of which she died. The history suggested an old syphilitic infection but no serological evidence of this was available, the blood Wassermann reaction being negative. Pathologically the condition was one of hydrocephalus due to obstruction of the foramina in the fourth ventricle by basal meningitis. Numerous miliary gummata were present over the pons and medulla.

Case 1.—M. R., a married woman, aged 39, was admitted to Hospital on June 18, 1928, under the care of Dr. Grainger Stewart. She complained of persistent headaches for the past five years, accompanied during the last ten months by vomiting. The headaches began on waking in the morning and were localized to the frontal and occipital regions. Occasionally double vision occurred on looking upwards and to the right. For about ten months hissing noises had been heard in the right ear accompanied by giddiness and a tendency to fall to the right side. Smells had recently become unpleasant, e.g., bread smelt like "mouldy cheese," a lighted cigarette like "burning rags."

Family history.—There was no evidence of syphilitic infection except that of her four children the third, a boy, aged 15, had "osteomyelitis" in "all the limbs" and was blind in the left eye. On examination the patient was mentally alert and co-operative. Her memory was good and she had no delusions or hallucinations. Speech was normal. The edges of both optic discs were blurred; in the right there were 2·5, and in the left eye 3·5 dioptries of swelling and in addition some fine streaky hæmorrhages in the retina. The pupils were equal, regular in outline and reacted to light and on convergence. No diplopia could be demonstrated. There was partial bilateral ptosis and the

patient complained that upward movement of the eyes made her feel sick. Very fine rapid horizontal nystagmus was present on full lateral deviation of the eyes, and was more marked in the left eye on looking to the right side. The corneal reflexes were diminished on both sides. There was a fine tremor of the outstretched hands and motor power was better in the left arm than in the right. The deep reflexes were grossly exaggerated but equal on the two sides. The left upper abdominal reflex was weaker than the right; both lower abdominal reflexes were absent. The plantar response was flexor on the right side and doubtful on the left. The gait was normal, but on looking upwards there was a tendency to fall backwards. The heart was not enlarged and the blood-pressure was normal (125 systolic, 80 diastolic). The liver and both kidneys were palpable. The Wassermann reaction in the blood was negative. The cerebrospinal fluid was not examined.

Whilst in hospital the headaches and vomiting became more severe. The knee and ankle jerks became brisker on the left side and the left plantar response became definitely extensor. A series of minor seizures without loss of consciousness or convulsions occurred and were followed a few days before death by definite epileptiform seizures with temporary loss of consciousness and rigidity of the limbs with the arms adducted and extended across the front of the trunk (c.f., tonic cerebellar fits). Two attacks of tetany, each lasting half an hour, occurred on July 18. The patient died on July 31, during an epileptiform seizure.

A post-mortem examination was made about twenty-four hours after death. The brain and cervical cord only were removed. On removing the calvarium, which was irregularly thickened, the convolutions appeared flattened. There was a moderate pressure cone. No tumour was visible on the surface of the brain. The membranes round the foramen of Magendie were matted together so that it needed considerable dissection to open into the fourth ventricle, which was then found to be dilated. There was also a dilatation of the third and lateral ventricles, though not of great degree. Over the front of the pons on the left side of the basilar artery were two sessile whitish cushions, about 2 mm. thick, in the pia arachnoid. The pia arachnoid was also thickened in both Sylvian fissures, depressing the brain tissue under it. Section of the brain at these areas, however, revealed no softening. The pituitary fossa was shallow, but the pituitary body was quite rounded and showed no evidence of compression. Similar arachnoidal thickening was found over the upper part of the cervical cord where little knots, several millimetres in thickness, were seen.

Histologically the condition was one of syphilitic meningitis. The small gummata over the pons were masses of thick fibrous tissue infiltrated with small round cells; in places they were necrotic, but not definitely caseous. The meninges were everywhere infiltrated with lymphocytes, and over the pons and upper part of the medulla contained numerous small gummata. Within these and also lying in clusters among the small infiltrating cells were many multinucleated giant cells in which the nuclei were distributed throughout the

cytoplasm. There was much perivascular infiltration of the meningeal vessels in this region, and many vessels showed hyaline degeneration of their walls. Round the upper part of the medulla and to a less extent over the ventral surface of the pons there were outgrowths of neuroglia through rifts in the pia mater. These were more numerous and larger than those in Case 4, but the neuroglial feltwork composing them contained fewer differentiated neuroglial fibrils; these were seen chiefly near the outer edges of the tufts. Numerous small tufts of neuroglia covered by ependyma projected into the fourth ventricle, which in its lower part appeared almost full of newly-formed neuroglial tissue.

Over the cervical cord the lymphocytic infiltration extended along the nerve-roots as well as into the walls of the meningeal vessels but it did not involve the walls of the vessels in the cord itself. The Weigert-Pal method revealed definite pallor of the column of Goll in addition to a generalized pallor of the periphery of the cervical cord. The nerve-cells in this region appeared healthy. No abnormalities were detected in sections from the frontal cortex or mid-brain, and except for perivascular infiltration of the vessels under the floor of the fourth ventricle the pons and medulla appeared normal. Perivascular infiltration with small lymphocytes was present round many vessels in the globus pallidus but not in other parts of the basal ganglia.

SUMMARY OF CASE 2.

A man, aged 30, suffered from headache, "vaso-vagal" attacks and an unsteady gait. His signs were those of a lesion in the fourth ventricle. The cerebrospinal fluid provided evidence of syphilis, and treatment was instituted. The patient died suddenly after a fit in his sleep. Pathologically internal hydrocephalus was present and numerous miliary gummata were discovered in the cerebellum.

Case 2.—J. E., a married man, aged 30, was admitted to hospital on September 12, 1929, under the care of Dr. Symonds. He complained of headache, "pins and needles" in the hands, fainting attacks and transient double vision. All the symptoms had been present for about three months. The headache was worse in the morning and the pain often extended to the back of the neck. The patient did not fall during or after the fainting attacks, but had noticed that his gait had become unsteady and his speech less distinct. In other attacks, which had occurred only at night two or three times a week for the previous three months, he felt "cold all over," broke out into a cold sweat and was unable to move a muscle; his mouth twitched on one side, and for about ten minutes he was unable to move a finger or to speak; in attempting to do so he only mumbled. There was no history of syphilitic infection. His wife had had no children, but one miscarriage.

On examination, the patient's speech was monotonous and rather indistinct. His memory and intellect were good. The pupils were equal, regular, and

reacted to direct and consensual light and on convergence. The optic discs were normal. The tongue was protruded to the right, and showed deep markings on its upper surface. Motor power was good, and the reflexes were unchanged. Sensation to pain and light touch was normal. Vibration was less appreciated on the right hand than on the left, was lost on the chest below the level of the nipple, felt over both great trochanters, but was absent below this level. His gait was unsteady with eyes closed, and he deviated to the right in walking. He was unable to stand on either leg alone. The size of the heart was within normal limits. The systolic blood-pressure was 130, the diastolic 70.

Cerebrospinal Fluid: Cells 260 per c.mm. chiefly small lymphocytes, 10 per cent. large mononuclears, 1 per cent. polymorphonuclears; total protein, 0.125 per cent.; Nonne Apelt positive, Pandy strongly positive; Lange 0001112110; Wassermann reaction positive, 4444 in fluid, 4444 in blood.

Whilst in hospital, he had several attacks of vomiting not associated with headache or giddiness. He was discharged from hospital on September 29, with the diagnosis of a lesion in the region of the fourth ventricle. On October 1, he came to hospital for the first injection of a course of nov-arsenobillon. He was well the next day, but on the night of October 3, he had a fit in his sleep and died immediately afterwards.

A report of the post-mortem examination performed for the inquest, stated that the convolutions were flattened, and that there was definite hydrocephalus. The arachnoid was thickened over the lower aspect of the cerebellum, and the fourth ventricle was dilated. No other abnormality was detected. The vessels were all healthy, and there was no naked-eye evidence of syphilis.

Through the kindness of the late Dr. Bronté, and of the Resident Medical Officer who attended the inquest, pieces of brain-stem and cerebellum were brought back to the Hospital for further examination. There were several areas of petechial hæmorrhage in the substance of the cerebellum which resembled bruising. No definite meningeal thickening was visible.

Microscopically, however, all the septa of the cerebellum showed considerable fibrous thickening of the arachnoid with numerous miliary gummata, both in relation to the small meningeal vessels (fig. 1), and also in many places in the cortex and subcortical white matter of the cerebellum. Some were surrounded by zones of small round cells, chiefly lymphocytes; others were free from infiltration. The gummata were composed of elongated endothelial cells, usually arranged in whorls round a small vessel. Giant cells with many nuclei, not necessarily peripherally placed, were seen in several of the larger gummata, and in the centre of others was a core of degenerated tissue. Occasionally, giant cells and degenerated tissue were present in the same gumma. In the areas of ecchymosis the chief change was a great dilatation of small vessels with perivascular infiltration by small lymphocytes. In the pons an occasional vessel was ringed with lymphocytes, but no miliary gummata were observed. As far as could be ascertained from the limited material at our disposal, the ependyma covering the floor of the fourth ventricle was in most

places free from exudate or neuroglial tufts, but in the lateral angles of the ventricle a few sub-ependymal granulations were visible.

SUMMARY OF CASE 3.

A man, aged 36, who admitted syphilitic infection, had the symptoms and signs of tabes dorsalis along with secondary optic atrophy, intense headache and vomiting. The latter symptoms were diagnosed as due to internal hydrocephalus. He died suddenly at home. The diagnosis was confirmed pathologically. There was intense gummatous meningitis and neuroglial proliferation in the floor of the fourth ventricle.

Case 3.—G. B., a married man, aged 36, was admitted to Hospital on June 30, 1926, under the care of Dr. Gordon Holmes. He had complained of headache for twenty-one months, of abdominal pain for three weeks, and of vomiting for a fortnight. The headache was localized to the back of the head and was worse at night. Vision had been poor in the right eye "for years," and was failing in the left. Difficulty in micturition had been noticed for five days previous to admission. He had acquired syphilis eight years before and had undergone a short course of treatment for this.

On examination, both optic discs were pale, the right more so than the left. The right pupil was larger than the left; both reacted to light and on convergence, but the left more sluggishly than the right. Muscular tone was diminished in the limbs. The knee and ankle jerks were absent and the plantar responses were flexor. The patient was an untrustworthy witness, but there seemed to be hypalgesia to pin-prick over the chest, the inner border of the arms, the outer side of the right leg and the inner side of the left leg. His gait was unsteady. No abnormalities were detected in the cardiac or respiratory systems.

Cerebrospinal fluid report: Whitish coagulum; cells 160 per cubic millimetre, 8 per cent. polymorphonuclears; total protein 0.05 per cent.; Nonne Apelt and Pandy positive; Lange, no change; Wassermann reaction positive, 4444 in cerebrospinal fluid and blood.

He was discharged from hospital on September 10, 1926, after a course of mercury and iodide, and was readmitted one month later on account of severe headache. He then had rigidity of the neck, pains in the arms and much vomiting. The right pupil did not now react to light. Cerebrospinal fluid report: Cells 12 per cubic millimetre; total protein 0.04 per cent.; Nonne Apelt and Pandy weakly positive; Lange 0112121000; Wassermann reaction positive 4321. A further course of mercury and iodide was given and he was discharged much improved on December 4, 1926.

On August 4, 1927, he was readmitted with a history of intense headache for nine weeks and vomiting of blood for a fortnight. Both optic discs now showed a post-papillitic atrophy. The left pupil was now larger than the right; both reacted to light through a small range, but better on convergence. The other signs remained the same. Cerebrospinal fluid report: Cells 60 per

cubic millimetre, 5 per cent. large mononuclears; total protein 0.085 per cent.; Nonne Apelt and Pandy very weakly positive; Lange 0011211000; Wassermann reaction positive 4444 in fluid and blood.

He was discharged from hospital on September 13, 1927, with the diagnosis of tabes dorsalis with internal hydrocephalus. He died suddenly at home on November 2, 1929. A post-mortem examination performed on November 5 by Sir Bernard Spilsbury was attended by one of us (J. G. G.). There were no external signs of disease. The brain and spinal cord were removed. A gummatous fibro-gelatinous meningitis was present over the base of the brain and the posterior surface of the cord, especially in the mid-thoracic region. On the ventral surface of the pons it covered the basilar artery so that this could barely be seen. There was, in addition considerable internal hydrocephalus affecting all the ventricles. No softening of the hemispheres or evidence of hæmorrhage could be seen. The arteries at the base of the brain were fairly healthy. The viscera all appeared healthy.

Histologically there was a diffuse syphilitic meningitis over the pons, medulla and spinal cord. Over the ventral surface of the medulla it formed a fairly dense layer of fibrous tissue. The superficial layer of neuroglia was here considerably proliferated and in places had burst through the pial covering to blend with the newly formed connective tissue. The blood-vessels in this region were thick-walled and dilated. There was a considerable degree of ependymitis, the floor in the lower part of the fourth ventricle being covered by neuroglial tissue which filled the calamus scriptorius and spread as an even layer for some distance on either side of it. The walls of several vessels underlying the floor of the ventricle were heavily infiltrated with small cells. There was also considerable infiltration and thickening of the spinal meninges, most intense over the cervical region. The vessels in the spinal cord itself were very thick-walled and widely dilated, but showed no perivascular infiltration. In the mid-dorsal region there was a small inflammatory focus in the anterior horn composed of a mass of small round cells bearing no relation to blood-vessels. There was a slight degeneration of the posterior columns of the cord, most evident in the middle root zone of the lumbar enlargement and only appearing in sections of the thoracic and cervical cord as a diffuse pallor.

The fibres of the optic nerve were almost entirely replaced by neuroglia and fibrous tissue.

SUMMARY OF CASE 4.

A woman, aged 30, had symptoms of increased intracranial pressure and signs which suggested a subtentorial lesion. Minor and major seizures occurred in hospital. On ventriculography the left ventricle contained more air than the right. No positive evidence of syphilis was obtained by an examination of the ventricular fluid and syphilis was not suspected from the history. The patient died following a subtentorial decompression. Pathologically the condition was one of obstructive

hydrocephalus, the fourth ventricle being lined by syphilitic granulation tissue which contained many miliary gummata and obstructed the foramina of Magendie and Luschka.

Case 4.—E. A., a married woman, aged 30, was admitted to hospital on February 10, 1930, under the care of Dr. Adie. For eighteen months there had been attacks in which the right hand "went dead" and in which she was momentarily unable to speak clearly. For seven months she had suffered from severe headaches, giddiness, vomiting and limpness of the arms. Latterly attacks of delirium had occurred during and after which she had been unable to see. Her health had otherwise been good except for "rheumatism" and there was nothing in the history to suggest previous syphilitic infection.

On examination she was found to be completely blind. The optic discs showed intense papilloedema with enormous retinal hæmorrhages. The right pupil was displaced upwards and inwards; it was small and very irregular in outline. The left pupil was larger, regular and circular. Both were inactive to light. There was complete paresis of the sixth nerve on the right side. The arms were hypotonic, inco-ordinate and tremulous on voluntary movement. The left knee-jerk was present, the right absent. The ankle-jerks were present and equal. Both plantar responses were extensor. The patient was doubly incontinent. Soon after admission she had a fit with loss of consciousness, and frequent attacks also occurred in which consciousness was not completely lost and from which it was possible to rouse her.

On February 27 a ventriculography was carried out which showed that the left ventricle contained more air than the right. The report on a specimen of ventricular fluid withdrawn at ventriculography was as follows: Cells 2·5 per cubic millimetres; total protein 0·02 per cent.; Nonne Apelt and Pandey negative; glucose 0·069 per cent.; Lange, no change; Wassermann reaction doubtful.

A subtentorial decompression was performed on March 4. The patient did not rally after the operation and died the same day. A limited post-mortem examination was carried out four hours after death, the brain only being removed. No tumour was found, but there was considerable hydrocephalus of all the ventricles, including the fourth. The meninges over the front of the pons and over the foramina of Luschka were considerably thickened. The foramen of Magendie was extremely small. The floor and roof of the fourth ventricle were granular. There was a greyish diffuse thickening of the pia arachnoid over both frontal lobes; the cortex here was thin and firm, and the pia mater unduly adherent. On section granular ependymitis was especially obvious in the fourth ventricle where the calamus scriptorius was filled up with exudate, but was also present in the lateral ventricles.

Histologically the whole surface of the fourth ventricle was covered by a layer of newly-formed tissue composed of fibroblastic and endothelial cells and containing a few giant cells and a number of lymphocytes. This overlay the ependymal layer which was broken in many places by tufts of neuroglia which projected into, and fused with, the new membrane. Immediately under the

ependymal layer the vessels were all intensely infiltrated and small gummata could be seen forming round many of these by proliferation of fibroblastic and endothelial cells; deeper in the tissues there was practically no perivascular infiltration or other alteration in structure. This condition extended as high as the iter of Sylvius but not into the lateral ventricles. In some places small gummatus nodules were formed in the new membrane and in many places giant cells lay free, or loosely attached, on the ventricular surface. A membrane of similar character filled the basilar cistern and covered the ventral surface of the upper medulla. It contained numerous miliary gummata with giant cells, and giant cells were also seen lying more diffusely in the superficial layers of the membrane (figs. 2 and 3). Some of them appeared to be almost free in the subarachnoid space. The pia mater in this region was broken through in several places by tufts containing a feltwork of fully differentiated neuroglial fibres which passed in between the gummata or merged with the overlying exudate. The roots of the seventh, eighth and ninth nerves as they passed out from the cerebellar-pontine angle were embedded in the exudate and a few giant-celled miliary gummata lay among the nerve-fibres. At a rather higher level, over the ventro-lateral surface of the pons, was a larger gumma, measuring 1.5 mm. transversely and rather less than 1 mm. in thickness. It was largely structureless but was penetrated by thin strands of collagen.

SUMMARY OF CASE 5.

A woman, aged 35, who had always been subnormal mentally and who had suffered from fits as a child, had symptoms of increased intracranial pressure and the signs of a left subtentorial lesion. Her mother had been under treatment for neurosyphilis for five years, and all except one of her five brothers and sisters had had fits as children. The patient died after a subtentorial decompression. At the autopsy, hydrocephalus of all the ventricles and a peculiar degeneration of the choroid plexus were found.

Case 5.—D. H., a single woman, aged 35, was admitted to hospital on July 27, 1930, under the care of Dr. Gordon Holmes. She had been completely blind for five weeks. She had complained of pain in the back of the head and neck for seven months, and of unsteadiness in walking with failure of vision for three and a half months. Amenorrhœa had been present for six months. She had always been mentally very backward and had had fits from birth until the age of 14, when they ceased with the onset of menstruation. The headache which dated from January, 1930, started in the back of the head and radiated forwards towards the eyes; it was worse on rising in the morning. In February, 1930, she had a fit lasting for thirty minutes during which she was unconscious but not convulsed. Subsequently the headache became more intense and generalized and was frequently accompanied by vomiting. The sight failed rapidly from March, 1930. Five weeks before admission she was noticed to have a rolling gait.

Family history.—Her father died of appendicitis at the age of 43. Her mother, aged 64, had been psychotic for about twelve years with visual hallucinations and delusions of grandeur. For the past five years she had been attending the Maida Vale Hospital for Epilepsy and Paralysis for courses of novarsenobillon. Of the four sisters of the patient, the two older, and one younger, had had fits as children, whilst her brother had had fits at the age of about 20, but was now apparently healthy and had two healthy children.

On examination the patient was found to be of inferior mentality. She was co-operative but not attentive. She perceived odours but could not distinguish essential oils from asafœtida. She had no perception of light. The optic discs were of a grey colour; there were a few small hæmorrhages in the right disc and about 2 dioptries of swelling; the left disc was swollen to 3 dioptries. The ophthalmological report (Mr. Paton) stated that there was more vascular change in the retina than was usual in cerebral neoplasms and suggested a syphilitic origin for the condition. The pupils were irregular and gave a slight unsustained reaction to light but no reaction on attempted convergence. A moderately fine, rapid nystagmus with the quick component to the left occurred on looking to the left, and a coarser, rotatory nystagmus on looking to the right. There was some impairment of upward conjugate movement, but no apparent paresis of the external ocular muscles. The right corneal reflex was more sluggish than the left. The jaw deviated to the right and the left masseter muscle contracted better than the right. There was no movement of the palate and the pharyngeal reflexes were absent. The right trapezius muscle was weak and the tongue deviated to the right.

Both flexion and hyperextension of the neck caused pain. Tone was diminished in the left arm and leg. There was some inco-ordination on both sides but more on the left than on the right. Perception of pain was generally impaired. The left arm reflexes were brisker than the right. The abdominal reflexes were sluggish, but better on the right side, while the knee and ankle jerks were brisker on the left side; the left plantar response was extensor, the right flexor. The apex beat of the heart was loud and sharp and preceded by a pre-systolic murmur. The Wassermann reaction in the blood was negative. A subtentorial decompression was performed on August 13. The patient died next day.

A post-mortem examination was made about twenty-four hours after death, the brain only being removed. There was considerable hydrocephalus of the lateral and third ventricles. The meninges over the base of the brain were considerably thicker than normal. On section a gelatinous exudate was seen on the floor of the fourth ventricle, so that the usual glossy appearance was lost. The calamus scriptorius also seemed to be filled up with this material. A slight degree of granular ependymitis was present in the lateral ventricles.

There was a localized swelling of each choroid plexus at the junction of the lateral and inferior horns of the lateral ventricles which was firm and yellowish in colour, and measured $1\frac{1}{2}$ cm. in diameter. Histologically they were composed of knots of varying size which consisted chiefly of laminated crystals of

cholesterin with a varying admixture of calcium salts surrounded by several layers of fairly thin connective tissue. Irritation giant cells were very abundant around the cholesterin plaques, passing in some distance between them. There was some small-celled infiltration around the vessels between these knots. Numerous corpora amylacea were present amongst the connective tissue of the plexus.

On microscopical examination the meninges over the pons and medulla were found to be thickened, but nowhere was there any evidence of either diffuse or perivascular cellular infiltration. The walls of many of the blood-vessels in the meninges over the base of the brain were thickened and appeared to be undergoing hyaline degeneration. There was no sub-pial overgrowth of neuroglia and the ependyma covering the floor of the fourth ventricle was fairly normal, but at the lower end of the calamus scriptorius it was covered in places by outgrowths of neuroglia. There was also slight granular ependymitis on the walls of the lateral ventricles. The blood-vessels in the neighbourhood of the ventricles were thickened but not infiltrated.

SUMMARY OF CASE 6.

A woman, aged 45, had symptoms of increased intracranial pressure. The cerebrospinal fluid afforded positive evidence of neurosyphilis, and after a course of treatment the symptoms were relieved. While in hospital she suddenly became drowsy, then comatose, and died suddenly after a convulsion. The foramina of the fourth ventricle were almost obliterated by arachnoidal adhesions, which caused obstructive hydrocephalus.

Case 6.—E. D., a married woman, aged 45, was admitted to Hospital, under the care of Dr. Gordon Holmes, on April 4, 1931. She complained of dragging of the left leg, pain in the back and unsteadiness in walking. All these symptoms had been present for about one month. For about five months she had had attacks of severe headache, localized to the back of the head, always worse in the morning, and occasionally accompanied by vomiting. The headache had recently become much more severe and the vomiting frequent and copious. For two weeks the vision had been failing, and, following an attack of double vision a few days previously, almost complete blindness supervened four days before admission to hospital.

Previous history.—In January, 1929, radium had been inserted into the cervix uteri for carcinoma.

On examination, she was extremely dull and unco-operative. She could read letters of one inch at a distance of two feet. The margins of the optic discs were blurred and there were about 2 dioptres of swelling in each. The retinal arteries were small and the veins engorged. The right pupil was larger than the left; both reacted to light, but the contraction was not maintained, and they reacted slightly on convergence. There was right-sided ptosis. No conjugate upward movement of the eyes was possible, and conjugate movement

to the left was weak. Nystagmus was present on looking to either side. The right side of the face was weak; the palate was drawn to the right, and the pharyngeal reflexes were absent. There was a rhythmical tremor of the outstretched hands. Both knee and ankle jerks were exaggerated. The right plantar response was flexor, the left extensor. The sense of position was lost in the left hand and impaired in the right. Joint sense was grossly defective in the hands and feet. Pain was everywhere well appreciated. She showed signs of meningeal irritability and stiffness of the neck. No abnormalities were detected in the cardiovascular or respiratory systems. Cerebrospinal fluid (April 8): Cells, 54 per cubic millimetre; 7 per cent. large mononuclears, 3 per cent. polymorphonuclears; total protein, 0.055 per cent.; Nonne Apelt weakly positive, Pandy positive; Lange, 4545533332; Wassermann reaction positive, 4442 in fluid, 4442 in blood.

After a course of six injections of novarsenobillon, her headaches became less severe, and the range of ocular movement less limited. A second report on the cerebrospinal fluid on May 26 was as follows: Cells, 47 per cubic millimetre, with 8 per cent. large mononuclears; total protein, 0.045 per cent.; Nonne Apelt negative, Pandy weakly positive, Lange, 4443432100; Wassermann reaction positive, 4420 in fluid, 4310 in blood.

On June 4, she suddenly became drowsy and quickly stuporose, and developed a right hemiplegia. She died later in the evening of respiratory failure after a sudden convulsion.

A post-mortem examination was made less than twelve hours after death. The skull was thin. The dura mater was tense over the vertex, and fenestrated over the frontal poles where the inner surface of the frontal bone was roughened and eroded in places. Over the middle cranial fossa the dura mater was thinned with small fenestrations through which the cerebral cortex was herniated. The arachnoid over the base of the brain was thick and tough, but its reticulum was not filled up or infiltrated. The cerebellar tonsils were glued to the dorsal surface of the medulla by firm arachnoidal adhesions so that there did not appear to be a cisterna magna. Over the left foramen of Luschka the arachnoid was ballooned out; over the right there were adhesions which seemed to obliterate it. There was no thickening of the arachnoid over the vertex of the brain. The ventricles were all greatly distended. Fine granulations were present in the lateral ventricles, but were not so obvious in the floor of the fourth ventricle. In the cervical region of the spinal cord the dura was adherent to the arachnoid. Elsewhere the arachnoid was thickened, and of a milky colour on both surfaces of the cord. Both middle cerebral arteries in the fissure of Sylvius were white, but had a lumen. The other arteries at the base of the brain were rather dilated, but not atheromatous. The lungs were healthy. The pericardium was adherent to the heart, which was enlarged, with thin, flabby, fatty walls. The valves appeared healthy. There was some atheroma round the origins of the coronary vessels, and very fine, streaky atheroma above the aortic cusps. The liver appeared healthy macroscopically, but microscopically was found to contain numerous miliary gummata. In the

aorta the vasa vasorum were thickened, but there was no perivascular infiltration and no infiltration of the media.

In the basal ganglia there were two triangular areas of intense gliosis, one in the innermost part of the globus pallidus, and the other just under the claustrum. In these areas there were many rod cells and enormous numbers of fibrous astrocytes with fairly thick processes. The blood-vessels in the vicinity were heavily infiltrated with small lymphocytes. The myelinated fibres passing through these areas of gliosis appeared normal; but that some destruction of myelin had taken place, was indicated by lipoid round the vessels, and the presence of numerous fat granule cells in sections stained by Scharlach R.

The cerebral meninges were diffusely thickened and infiltrated in the sulci. The vessels running into the medulla were hyaline, their walls were infiltrated, and they were surrounded by many corpora amylacea. There was considerable proliferation of the subependymal neuroglia in the lateral and fourth ventricles. The ependyma in the lower part of the fourth ventricle was covered by a new layer consisting chiefly of neuroglia, but in some places also containing collagen fibres. Hyaline changes were found in the walls of the vessels under the floor of the fourth ventricle, and the choroid plexus in this situation contained many calcified nodules. The spinal meninges were thickened, and an occasional fibrous knot, ringed with lymphocytes, was present over the cervical region of the cord. In Weigert Pal preparations of this level the column of Goll was pale, and in sections stained by Mallory's method a neuroglial overgrowth was visible. In the eighth cervical and first dorsal segments, the anterior horn cells were rounded, shrunken and vacuolated.

SUMMARY OF CASE 7.

A man, aged 44, who admitted venereal infection, gave a history of fits and difficulty in walking. His signs were those of a tetraplegia accompanied by multiple cranial nerve palsies. He died of hypostatic pneumonia and pathologically there was hydrocephalus due to obstruction of the foramina in the fourth ventricle by syphilitic granulation tissue containing miliary gummata. A large meningeal gumma was present over the upper cervical region of the cord.

Case 7.—E. H., a married man, aged 44, was admitted to Hospital on October 6, 1922, under the care of Dr. Aldren Turner. In 1903 he had acquired venereal disease and had been treated for a few weeks. In 1917 he had two attacks of unconsciousness, each lasting two minutes, and since then had complained of difficulty in walking, pains at the back of the neck, a sensation of "pins and needles" in the hands and attacks of trembling and giddiness. Recently bladder control had been lost.

Examination: The patient was a well-nourished man. His memory, though good, had deteriorated. His speech was normal: his smell was defective. His vision was $\frac{1}{8}$ in the right eye, $\frac{2}{8}$ in the left. The optic

disks were pale and the right was a little blurred. The pupils were equal, central and regular; they reacted to light but quickly dilated, and reacted to accommodation. Lateral deviation of the eyes to the left was difficult and on extreme lateral deviation there were coarse irregular nystagmoid jerks. The left eye seemed more prominent, and there was less retraction of the left eyelid than of the right. The right masseter and temporal muscles were weak. Both corneal reflexes were brisk. There was slight weakness of the left orbicularis oculi. The tongue was protruded to the right; it showed a slight tremor, but no atrophy. The right grasp was stronger than the left. Co-ordination was poor in all limbs. Sensation to pain and light touch was unimpaired, but muscle sense, vibration and the sense of position were lost in the arms and legs. The deep reflexes were brisk and equal. The plantar responses were flexor. The gait was ataxic and the toes of the right foot were dragged along the ground. The cardiovascular and respiratory systems appeared healthy.

Cerebrospinal fluid: Cells 33 per cubic millimetre, consisting of large and small mononuclear cells and about 15 per cent. of polymorphonuclear; total protein 0.05 per cent. Nonne Apelt positive; Lange 0223422110; Wassermann reaction positive, 4444 in cerebrospinal fluid, 4320 in blood.

During the last week in December, 1922, sudden weakness of the right arm and leg developed, followed a week later by weakness of the left arm and leg. On January 8, 1923, the pupils were irregular, the left larger than the right; they still reacted to light. There had been occasional diplopia. On lateral deviation of the eyes there was now well-marked nystagmus, rapid on looking to the right, slow on looking to the left. The area supplied by the left fifth nerve, and by the second and third divisions on the right side, were analgesic. The right side of the face was weak and the sense of taste was lost. The patient was deaf in both ears and had vertigo, objects rotating to the right side. There had been occasional dysphagia, but the palate moved well. Both arms were spastic and were flexed across the chest. The right arm and leg were completely powerless. All movements of the left arm and leg were possible but weak. A to-and-fro tremor was present occasionally in the right arm, and involuntary jerking of the right arm and leg caused the patient much annoyance. Even more troublesome was a jerking of the left leg, which occurred only at night and which was followed by pain. A persistent dull pain radiated from the seventh cervical spine to the front of the chest, and there was some hyperæsthesia over this area. The sense of pain and light touch was almost completely lost over the whole of the left side of the body below the clavicle. All the reflexes were exaggerated and both plantar responses were now extensor. During the remainder of January the patient became weaker and signs of hypostatic pneumonia appeared in the lungs. His neurological signs remained unchanged till he died on January 31.

A post-mortem examination was made twenty-four hours after death. The brain and spinal cord were removed together with the left retina and optic nerve and the contents of the right orbit. At the base of the brain and over

the cervical region of the cord the dura mater was extremely adherent to the pia arachnoid. No cisterna magna could be made out, all the membranes being matted together. The medulla was softened, greyish in colour, and flattened by distension of the fourth ventricle. There was much hydrocephalus. Except at the base of the brain and over the cervical region of the cord, there was no adhesion between the arachnoid and the dura; and the dura was nowhere thickened. The spinal cord was pale, swollen and softened in the cervical region. A few small gummata were present on the posterior surface of the cord, one at the origin of the roots of the cauda equina being especially large. The upper cervical cord was grossly distorted through compression by a gumma in the meninges on the postero-lateral aspect of the cord, measuring 9 mm. in transverse diameter and 5 mm. in thickness. Its outer part was firm and fibrous; its central part, caseous and necrotic. The meninges in this region were enormously thickened, measuring about 3 mm. in diameter.

Histologically there was fairly severe infiltration of the cortical meninges, especially in the depths of the sulci, but the cortical vessels although thickened were not infiltrated. Granular ependymitis was seen in the lateral ventricles and there was slight infiltration of many of the small sub-ependymal vessels. In the mid-brain and pons all the vessels were dilated and thickened, and those under the ventricular surface were surrounded by wide cuffs of lymphocytes. In the iter and on the floor of the fourth ventricle the ependyma was covered by a thick layer composed partly of neuroglial elements in which fibrils could be demonstrated, but mainly of a cellular connective tissue. There was considerable proliferation of the sub-ependymal neuroglia in this region and in many places the line of ependymal cells was broken. The calamus scriptorius was filled up by a mass consisting partly of neuroglia which had overgrown the ependyma, and partly of the choroid plexus which was infiltrated with small cells and contained several miliary gummata. Dense perivascular infiltration and a few miliary gummata were also seen under the floor of the ventricle in this region.

The pia-arachnoid was infiltrated and thickened over the pons and medulla. On the dorso-lateral surface of the medulla at its lowest level there was a remarkable outgrowth of neuroglia into the meninges, so that a superficial zone was formed in which areas of neuroglia were intersected and penetrated by collagen fibres (fig. 4). There was also in this region, especially near the median raphe, considerable overgrowth of connective tissue round the walls of the vessels, the new fibres being chiefly arranged parallel to the vessel walls, but short radial projections also extended from them into the nervous tissue.

In addition to the large gumma in the meninges of the upper cervical cord, several smaller gummata were also seen in this region and large masses of lymphocytes were scattered throughout the meninges in all regions of the cord. Many of these were localized round blood-vessels and probably represented an early stage in gumma formation. The vessels in the cord were

thickened and widely dilated; but no perivascular infiltration was seen inside the cord. In the upper cervical region where the cord was compressed and distorted it was difficult to identify the various fibre tracts by the Weigert Pal method, but as far as could be ascertained the chief loss of myelin was around the periphery of the cord, an appearance to which the name of "syphilitic halo" has been given. This appearance was even more evident in lower segments of the cord where the pallor at the periphery contrasted strongly with the well myelinated fibres in the central zones (figs. 6 and 7). The nerve-roots throughout the cord, even in that portion which was compressed by the gumma, were well myelinated.

The retina and left optic nerve appeared normal except for slight oedematous changes at the nerve head.

DISCUSSION.

It has already been noted that Oppenheim, under the heading of "Diffuse Gummatus Meningitis," described a clinical picture which resembles closely that presented by our cases. The salient points in this syndrome are early headache, later vomiting and vertigo, with attacks of loss of consciousness or general convulsions, a moderate degree of dementia with failure of memory and apathy, attacks of stupor lasting for several hours or days and separated by long intervals of full consciousness, paralysis of various cranial nerves, especially those of the eye, and commonly papilloedema and consecutive optic atrophy. He considered that these symptoms were caused by widespread basal meningitis. But loss of consciousness, attacks of stupor and reduction of intelligence suggest a more general affection of the brain, of which the most probable cause is increase of intracranial pressure. Headache and papilloedema are probably also caused by hydrocephalus, although they might possibly be due to more local conditions. On the other hand basal meningitis is certainly the cause of the cranial nerve palsies which are so constantly present, and which, by their protean nature, distinguish syphilitic hydrocephalus from other forms of intracranial hypertension.

Headache was present in all our cases and was usually the first symptom. In one case it preceded all other symptoms by four years; in the others it was associated soon after its onset with other symptoms, of which the most common were diplopia and attacks of various kinds. It was often severe and resembled the headache of cerebral tumour in being accompanied by vomiting, giddiness, or difficulty in walking. Most commonly the headache was localized in the back of the head and the neck. That it was due to intracranial hypertension was indicated,

in some cases, by the early presence of papilloedema and consecutive optic atrophy.

Attacks of loss of consciousness, sometimes convulsive in character, occurred during the course of the illness in four cases, and terminal convulsions were present certainly in one, and probably in two of the others. In Cases 1 and 2 some of the attacks were of an unusual character. In Case 1 there were purely tonic fits, with temporary loss of consciousness, in which the arms were adducted and extended across the front of the trunk. These attacks may have had some relation to tetany, of which also the patient had two attacks. In Case 2, seizures occurred which were typical instances of the "vaso-vagal attacks" described by Gowers. In these the patient felt cold all over, broke out into a cold sweat, and for about ten minutes, although perfectly conscious, was unable to move a muscle or to open his mouth to speak. Gowers attributed attacks of this kind to an affection of the medulla, and, although we were unable to confirm this owing to the limited pathological material at our disposal, it is significant that in this case the meningitis round the foramen of Magendie was more intense and acute than in any of the others. In only one of our cases (Case 5) were there attacks of complete loss of consciousness without convulsions, but in Case 4 there were somewhat similar attacks in which consciousness was not completely lost, so that the patient could be roused. In no case were there prolonged attacks of stupor such as Oppenheim describes, but in Case 6 there was extreme mental dullness throughout the three months that the patient was in hospital.

Cranial nerve palsies were prominent in every case and instances of paralysis of each individual cranial nerve were encountered. Oculomotor palsies were the most common, occurring in all except Case 2. In Cases 1, 2 and 6, diplopia was one of the early symptoms. Defective upward movement of the eyes was noted in three cases and ptosis, inequality of the pupils, strabismus and nystagmus were also seen. These oculomotor palsies were often combined with weakness of the jaw, face, palate, pharynx or tongue, usually greater on one side. This association indicated a widespread affection of the basal meninges which was actually found at the post-mortem examination.

Papilloedema was present in all except Case 2, and in four cases had progressed to optic atrophy. In two cases blindness had set in rapidly becoming complete in one of these within two weeks after diminution of vision was first noticed. In Case 5, in which the syphilitic infection was probably congenital, there were, in addition to "secondary"

atrophy, vascular changes in the retina of a syphilitic nature. While it is unsafe to suppose that every syphilitic patient who has papilloedema is suffering from hydrocephalus, it seems probable that in this series of cases the papilloedema and optic atrophy were due rather to the general increase of intracranial pressure than to meningeal inflammation around the optic nerves. In the only case (Case 3) in which there was gradually progressive optic atrophy, the patient had severe headaches between his periods of hospital treatment, and the appearance of his optic discs was that of post-papillitic rather than of "primary" optic atrophy. It is possible that in his case the local sclerosis of tabetic atrophy combined with the increase of intracranial pressure to destroy the optic nerve.

Weakness or sensory disturbances in the trunk and limbs were not prominent in our cases, although in one case there was a severe tetraplegia due to meningomyelitis of the cervical cord. In three a slight degree of hemiplegia was present, and it is noteworthy that in none of these did the distribution of paralysis in the cranial nerves suggest a cortical or capsular lesion; and, in effect, no lesion above the brain-stem was found in them. The only foci of cerebral softening found in our cases were two minute areas in the lenticular nucleus in Case 6, and these apparently had not given rise to any symptoms.

The unsteadiness of gait, and inco-ordination, limpness and weakness of the arms from which several of the patients suffered are not easily explained on a pathological basis. To some extent they may have been due to the hydrocephalus, but in several cases the presence of vertigo, nystagmus or gross ataxy of the arms suggested a lesion of the vestibulo-cerebellar system. Except in Case 2 there was no pathological evidence of damage to the cerebellum or the deeper tracts of the brain-stem, although the most superficial fibres undoubtedly suffered in some cases; on the other hand, there was considerable cellular infiltration, and sometimes gummatous formation, in the sheaths of the eighth nerves. It seems therefore possible that these symptoms were due, at least in some cases, to injury of the vestibular nerve; in Case 1 this was rendered still more likely by the association of tinnitus with the attacks of giddiness.

PATHOLOGICAL ANATOMY.

The most important question that arises in a survey of the pathology of these cases is the mechanism of the hydrocephalus. To gain an exact knowledge of this under the conditions of an ordinary post-mortem

examination may be difficult or even impossible when the hydrocephalus is of the communicating type. Penfield and Elvidge have suggested injecting a suspension of indian ink under pressure into the ventricles, as soon after death as possible, and determining the position of the block in the subarachnoid space at the subsequent post-mortem examination by the staining of the meninges. Unfortunately, we did not know of this technique at the time of autopsy nor was hydrocephalus suspected in any of the cases in which the autopsy was performed at the National Hospital. While the presence of arachnoidal thickening round the pons and in the cisterna basalis suggests an obstruction to the passage of cerebrospinal fluid from the posterior to the middle cranial fossa, it is impossible to determine the degree of obstruction after the brain has been removed from the skull. Even Penfield and Elvidge's method gives little indication of the defect in the absorption of cerebrospinal fluid, although from Dandy's classical experiments it may be assumed that hydrocephalus will result whenever the passage of fluid from the posterior to the middle cranial fossa is completely blocked. Even an incomplete block in this situation would probably produce some degree of hydrocephalus, and certain of the milder syphilitic cases which yield to medicinal treatment are no doubt caused in this manner.

Narrowing of the foramina of Magendie and Luschka is a more obvious cause for hydrocephalus, and its effect in obstructing the passage of fluid is easier to assess. But after the brain has been hardened in formalin it is almost impossible to ascertain the condition of these foramina. We were able to make a careful examination of the foramina at the autopsy in four of our cases, but in Case 2, an inquest case, and in Case 5, in which the autopsy was performed during a holiday period, no such examination was made. In Case 3, there was no obvious blockage of the foramina; as this patient had benefited considerably from three periods of hospital treatment which included lumbar puncture, it seems likely that here the hydrocephalus was of the communicating type.

In the other four cases (1, 4, 6 and 7) there was very definite evidence of blockage of the foramina of exit from the fourth ventricle. The usual condition in these cases was that the cerebellar tonsils were glued down over the back of the medulla obstructing the foramen of Magendie, and that the foramina of Luschka were obliterated by meningeal thickening, the fourth ventricle was ballooned out and the cisterna magna was empty. It is probable that the closure of the foramen of Magendie was caused to some extent by the intense granular

ependymitis, which had filled up the calamus scriptorius with newly formed tissue.

It is unfortunate that no special examinations were made during life in any of our cases to determine the freedom of communication between the ventricles and the lumbar theca. From the point of view of treatment this knowledge is of the greatest value, as it is improbable that cases of non-communicating hydrocephalus can be saved by lumbar puncture and anti-syphilitic treatment alone. Even in Case 3, which was probably of the communicating type, this treatment did not prevent progressive blindness and eventual death. In Cases 1, 4 and 5, lumbar puncture was not performed and the true nature of the condition was not diagnosed. In two of these (Cases 1 and 4) the Wassermann reaction was negative in the blood although in Case 1 there were gummata, both of the giant-celled and necrotic types, in the meninges. In Case 4, where the infection was probably congenital, no progressive syphilitic lesions were present in the nervous system, and had it not been for the family history and the knowledge that the patient's mother was undergoing anti-syphilitic treatment the diagnosis would have been difficult even after a histological examination of the brain.

The *microscopical study* of these brains brought out two features in the histopathology of tertiary neurosyphilis which seem to be somewhat neglected in descriptions of the disease. These were (1) the intensity of the neuroglial reaction round the medulla both on its ependymal and pial surfaces, and (2) the frequency with which giant-cells were present in the syphilitic granulation tissue.

(1) *Granular ependymitis* is well known to occur in general paralysis as small discrete projections of neuroglia through the ependymal lining of the ventricles. In most of our cases however, the ependymitis was much more intense, so that a gelatinous mass filled up the calamus scriptorius and was spread in a thin layer over the lower part of the ventricle, completely covering the ependyma. The frequency with which the subependymal vessels were heavily infiltrated with lymphocytes indicated the inflammatory nature of this new membrane. In Cases 4 and 7 this was very evident. Here the new membrane was composed not so much of neuroglia as of fibroblastic and endothelial cells with, in Case 4, numerous giant-cells and minute gummata; in the latter case it completely covered the walls of the fourth ventricle up to the iter of Sylvius. The condition resembled fairly closely that which may be seen in tuberculous meningitis, except that it was of more chronic nature with a considerable overgrowth of neuroglial fibres in the

deeper layers of the membrane. It was quite evident in these cases that inflammation from the basal meninges had spread into the fourth ventricle and permeated it from below upwards; and it is probable that the pathogenesis of the neuroglial overgrowth in the other cases was similar although in them the inflammation was less acute.

Less attention has been paid to the neuroglial outgrowths through the pia mater over the ventral surface of the medulla. These were described and figured by Purdon Martin in syphilitic amyotrophy, and by Lhermitte in tertiary neurosyphilis. They were seen in four of our cases, and are probably fairly common in gummatous basal meningitis. Like the ependymal granulations they appear to be of inflammatory origin, the proliferation of the subpial neuroglia being stimulated by chronic inflammation in the pia-arachnoid. Whether the rifts in the pia mater are primary or secondary is a difficult question to decide. It seems most probable that they are directly due to the inflammatory changes in this membrane, since the subpial neuroglia almost constantly proliferates in cases of syphilitic meningitis, but rarely bursts through the pia mater. Further evidence of the inflammatory nature of the neuroglial overgrowth is provided by the presence of cuffs of lymphocytes around the subpial vessels in the more acute cases.

The marginal pallor of the cord in Weigert-Pal sections, to which the name "syphilitic halo" has been given, is clearly of similar origin. For this we must postulate a progressive destruction of the myelinated fibres which lie nearest to the inflamed pia mater by toxins passing inwards from this membrane. This marginal degeneration is not uncommonly present in long-standing cases of syphilitic meningitis. It was well described and figured by Purdon Martin in syphilitic amyotrophy, and Léri also mentioned it as occurring in that condition. It was present in only two of our cases and therefore appears to be less often met with in the more acute and diffuse forms of syphilitic meningitis than in syphilitic amyotrophy, in which, in our experience, it is almost constantly present. It is noteworthy that these were the only two cases in which the gummata in the meninges were large enough to be visible to the naked eye. Even in these they were of small size, the largest, that on the cervical cord in Case 7, being only about one centimetre in diameter and half a centimetre in thickness.

(2) *Giant-celled gummata* of minute size were present in Cases 1, 2 and 4, and were the most striking feature of the inflammation in Cases 2 and 4. In Case 6 they were found in the liver only. Jakob has recently drawn attention to their common occurrence in syphilitic meningitis, and

has demonstrated them also in the cerebral cortex. It is probable that the comparative rarity at the present time of the larger meningeal gummata, and the frequency with which these minute gummatous formations are found, may be correlated with the alterations in therapy which have taken place during the last twenty years. Treatment with arsenic and bismuth does not appear to have greatly influenced the incidence of neurosyphilis, but it does seem to have reduced the size of gummata in the nervous system and probably also throughout the body.

From a histological examination alone it is often difficult to distinguish the condition of the meninges and the floor of the fourth ventricle in a case such as E. A. (Case 4) from that seen in tuberculous meningitis. The most important distinction is that the nuclei of the syphilitic giant-cells are usually present throughout the cell body and are not, as in tuberculous giant-cells, confined to the periphery. Jakob lays considerable emphasis on this distinction. There is also a much greater tendency for collagen fibres to be present in a syphilitic gumma. Still more important is the discovery of the causative organisms in the nodule. While it is usually possible to see tubercle bacilli in giant-celled tubercle nodules, spirochaetes are not often found in miliary gummata; we were unable, in spite of careful search, to find them in any of our cases. But the knowledge that the Wassermann reaction is positive in both blood and cerebrospinal fluid, as in Case 2, makes the diagnosis reasonably certain.

Conclusions.—(1) Hydrocephalus is a fairly common result of basal gummatous meningitis. Although it is usually of the communicating type, complete obstruction of the foramen of Magendie is not uncommon, and the foramina of Luschka may also be sealed up by plastic meningitis. (2) At the present time syphilitic hydrocephalus is a more common post-mortem finding than the larger syphilitic gummata of the meninges on which more emphasis was laid in the past. Minute gummata, sometimes of the miliary giant-celled type, are often present in hydrocephalic cases. (3) The endymenitis and extra-pial outgrowths of neuroglia associated with gummatous meningitis are direct results of inflammation in relation to these membranes. Degeneration of the myelinated fibres on the surface of the spinal cord also occurs in long-standing cases.

We desire to express our thanks to the medical staff of the National Hospital, Queen Square, for permission to use the clinical records of the Hospital, and especially to thank Dr. James Collier and Dr. Gordon Holmes for their helpful interest.

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BIBLIOGRAPHY.

- [1] COLLIER, J., and ADIE, W. J. Price's "Textbook of the Practice of Medicine," 3rd Edition. Oxford and London, 1930.
- [2] GOWERS, W. R. "A Manual of Diseases of the Nervous System," 2nd Edition. London, 1898.
- [3] *Idem*. "Syphilis and the Nervous System." London, 1892.
- [4] *Idem*. "The Borderland of Epilepsy." London, 1907.
- [5] IBRAHIM, J. Pfundler and Schlossmann's "Handbuch der Kinderheilkunde," 4th Edition. Berlin, 1931.
- [6] JAKOB, A. "Normal und Pathologische Anatomie und Histologie des Grosshirns." Leipzig und Wien, 1929.
- [7] JEANS, P. O., and COOKE, J. V. "Prepubescent Syphilis," in "Clinical Pediatrics." New York and London, 1930.
- [8] LÉRI, A. "Les Atrophies Musculaires Syphilitiques," in "Questions Neurologiques d'Actualité." Paris, 1931.
- [9] LIEBRICH, J. "Le gliose extra pie-mérienne bulbo-spinale dans les affections syphilitiques du système nerveux," *Annales d'Anatomie Pathol.*, 1926, **3**, 118.
- [10] MARTIN, J. PURDON. "Amyotrophic Meningo-myelitis," *Brain*, 1925, **48**, 153.
- [11] NONNE, M. "Syphilis und Nervensystem," 5th Edition. Berlin, 1924.
- [12] OPPENHEIM, H. "Lehrbuch der Nervenkrankheiten," 7th Edition. Berlin, 1928.
- [13] PENFIELD, W. G., and ELVIDGE, A. R. "Cytology and Cellular Pathology in the Nervous System," **3**, 1931. New York, 1932.

PLATE LEGENDS.

FIG. 1 (*Case 2*).—Section of cerebellar cortex. Several small giant-celled gummata are present in the pial septa, and minute early gummatous formations are seen along the lines of the small vessels in the molecular layer of the cortex. *m* = molecular layer; *g* = granular layer; *p* = pial septa.

FIG. 2 (*Case 4*).—Lateral surface of medulla. Four small gummata surrounded by darkly staining neuroglia fibres are present in the inferior medullary velum. The pial septum is heavily infiltrated with small cells. (Mallory's phosphotungstic acid hæmatoxylin stain.)

FIG. 3 (*Case 4*).—Ventricular wall of the fourth ventricle. Two giant cells lie free on the surface. A small gumma and a heavily infiltrated vessel are seen just under the line of the ependyma.

FIG. 4 (*Case 7*).—Dorso-lateral surface of medulla. The darkly staining fibres of the pia mater are seen irregularly penetrating the paler neuroglial outgrowths. The entering vessels near the dorso-mesial septum are thickened and infiltrated.

FIGS. 5 AND 6 (*Case 7*).—Sections of cervical and lumbar enlargement of cord showing peripheral zone of demyelination. The nerve-roots at the cervical level are darkly stained. (Weigert-Pal method.)

PLATE XII.

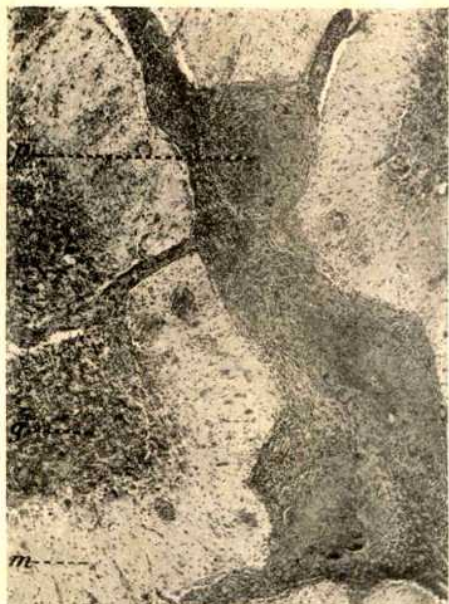


FIG. 1.

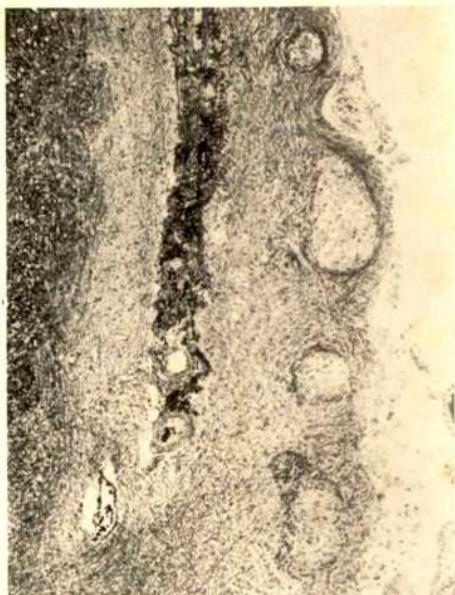


FIG. 2.

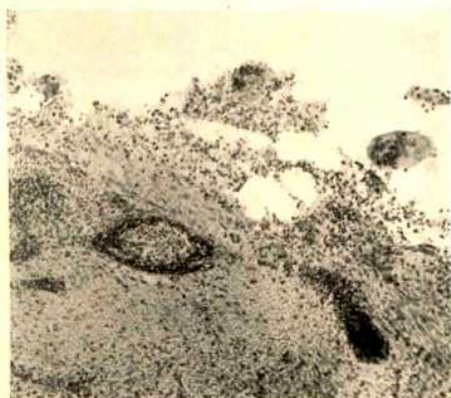


FIG. 3.

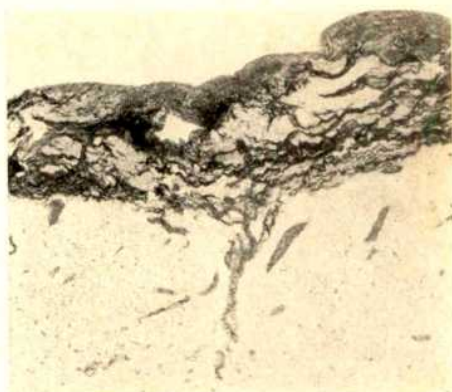


FIG. 4.

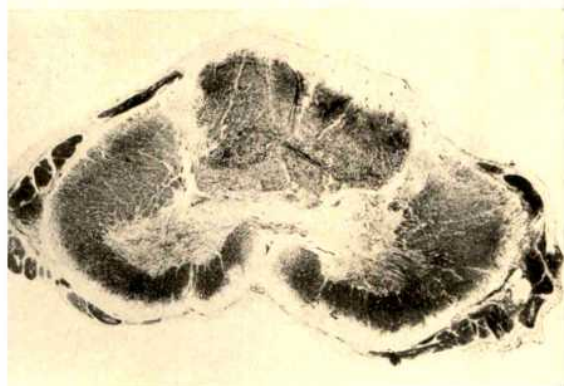


FIG. 5.

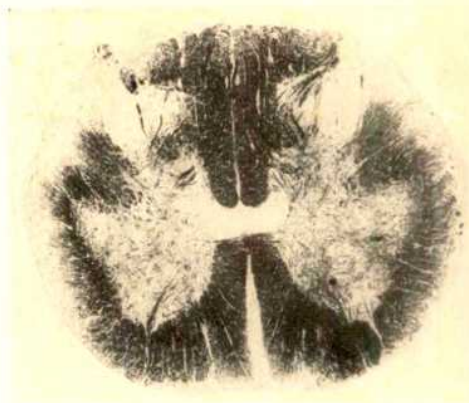


FIG. 6.

ON THE PHARMACOLOGY OF THE GRASP REFLEX.

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Baltimore, Md.*

KNOWLEDGE regarding the mechanisms involved in the grasp reflex is still very limited, all data available at present having been obtained from two sources: the normal newborn infant, and the adult with lesions of the frontal lobes of the brain or underlying structures. It is a well-known fact that the human infant shows this reflex for several months after birth, usually until voluntary grasping begins. After that, this phenomenon seems never to appear spontaneously again, except with destruction of the cerebral areas already mentioned. It has been demonstrated in previous papers, however, that a reflex grasping response can be induced in adult monkeys by hypodermic injection of bulbocapnine (Richter and Paterson, 1931), and by inhalation of carbon dioxide gas in high concentrations (Richter and Paterson, 1932). On the basis of these observations, it seems possible that the pharmacological aspects of the problem may prove very significant. From this point of view, the above experiments have been repeated with several other drugs to determine whether the reflex can be brought out by any agents besides bulbocapnine and carbon dioxide, and if so, by any special group of such agents.

METHODS.

All of the monkeys used in these experiments were of the *Macacus rhesus* species and had attained at least half their full growth. The technique for eliciting and measuring the reflex in adult animals, described in detail in previous papers, is based upon the fact stated above, that a normal monkey beyond infancy will not hang from a horizontal bar placed within its grasp (Richter, 1931). However, an adult animal in which the reflex has been elicited by some abnormal condition will grasp the rod and hang from it by one hand for an

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appreciable length of time. This time interval may be regarded as a measure of the strength of the reflex.

In order to simplify the procedure, both legs and one arm were tied and one hand left free for testing. The two hands were tested alternately at frequent intervals following the administration of the different drugs.

These were given in varying strengths, usually up to the minimum lethal dose, most of them by hypodermic injection, but some of them orally, intravenously, or intraperitoneally.

RESULTS.

Sixteen of the twenty-three drugs used in these experiments produced a condition in which the grasp reflex could be elicited. These drugs, showing in common a depressant action on the cerebrum, all caused either an absolutely stuporous state or at least a condition in which there was a marked reduction of responsiveness. Whilst many of these agents are primarily cerebral depressants, some of them are stimulants (e.g., carbon dioxide), and have a depressant action only when given in large doses. Administration of small doses results in a state of cerebral stimulation and the reflex cannot be elicited. The remaining seven drugs have either a stimulating effect on the cerebrum or a limited peripheral action.

The twenty-three drugs used in these experiments are listed in Table I, together with the following data: the method of administration and dosage per animal; a record of the presence or absence of the reflex; the time in seconds during which it occurred; and the longest single response recorded in each experiment. It will be noted that with the exception of bulbo-capnine, all of the drugs were given in doses very large in proportion to the size of the animals. Only one animal was lost during the entire series of experiments; that was due to the effect of camphor. A wide range of variation in response to the different drugs is at once apparent from the table. These variations are brought out more clearly in the following charts.

After the administration of bulbo-capnine, the reflex quickly reaches maximum strength and then gradually decreases until it disappears entirely. The bulbo-capnine curves are consistently very smooth and regular, as may be seen in fig. 1 A, in which the strength of the reflex as measured by the hanging time in seconds is presented on the ordinates and the duration of the experiment in minutes on the abscissæ. Before the injection (50 mg. of bulbo-capnine) the hanging

response was absent; twenty minutes afterwards the response had reached a maximum for both hands, and fifty-five minutes later still it had entirely disappeared again.

TABLE I.

Agent	Mode of administration	Dosage per animal	Reflex present	Greatest interval in minutes during which hanging response was present	Longest hanging time in seconds
1. Bulbocapnine..	Subcut. inject.	10-100 mg.	+	450	92
2. Carbon dioxide	Inhalation	15-50 % 2-10 minutes	+	45	90
3. Ether	Inhalation	3 minutes	+	5	88
4. Amytal	Intraper. and intraven. inject.	0.5-1.5 c.c. 10 % sol.	+	320	57
5. Chloral hydrate	Intraper. inject.	500 mg.	+	240	2
6. Paraldehyde ..	Stomach tube	2.5 c.c.	+	420	65
7. Luminal	Subcut. inject.	580 mg.	+	320	8
8. Morphine	Subcut. inject.	84 mg.	+	120	6
9. Apomorphine ..	Subcut. inject.	17 mg.	+	20	20
10. Cocaine	Subcut. inject.	30 mg.	+	12	15
11. Hyoscine	Subcut. inject.	10 mg.	+	100	10
12. Alcohol	Stomach tube	50 c.c. 50 % sol.	+	320	30
13. Insulin.. ..	Intraven. inject.	12 units	+	60	41
14. Camphor	Subcut. inject.	10 c.c. 20 % sol.	+	480	61
15. Eserine	Subcut. inject.	2.5 mg.	+	100	28
16. Strychnine ..	Subcut. inject.	2.2 mg.	+	80	9
17. Adrenalin	Subcut. inject.	2 c.c. 1:1,000	—	0	0
18. Atropine	Subcut. inject.	2.8 mg.	—	0	0
19. Pilocarpine ..	Subcut. inject.	6 mg.	—	0	0
20. Pituitrin	Subcut. inject.	2 c.c.	—	0	0
21. Caffein.. ..	Subcut. inject.	120 gr.	—	0	0
22. Nitroglycerine.	Subcut. inject.	1.4 mg.	—	0	0
23. Histamine	Subcut. inject.	12 mg.	—	0	0

Inhalation of carbon dioxide had much the same effect, but for a shorter length of time—a fact to be expected, since the carbon dioxide was administered in gaseous form and could thus escape more readily from the body. In fig. 1 B, it can be seen that the effect reached a maximum of sixty-five seconds, but persisted for only five minutes, in comparison to ninety minutes under the influence of bulbocapnine. A similar record, obtained during ether anæsthesia, is presented in fig. 1 C.

Alcohol produced a somewhat different type of curve. In fig. 2 A it can be seen that the reflex was present for four hours, remaining fairly constant throughout the entire time, but it never reached a level as high as with bulbocapnine, carbon dioxide, or ether.

Paraldehyde gave still another type of record, with the reflex very strong occasionally, but fluctuating widely from moment to moment, and sometimes actually difficult to elicit. A fairly typical record is presented in fig. 2 B. This animal received 2.5 c.c. of paraldehyde.

The records obtained after injection of amytal are interesting because of the light they may possibly throw on the relation of the reflex to sleep. In a typical experiment recorded in fig. 2 C, the reflex

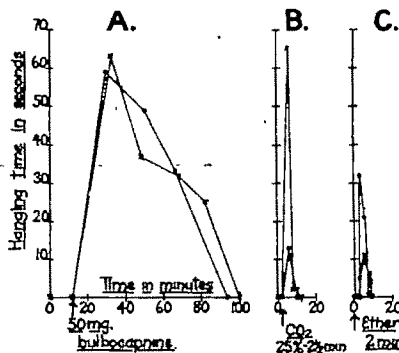


FIG. 1.—Graphs showing the effect of (A) bulbocapnine; (B) carbon dioxide gas, and (C) ether on the hanging response. The magnitude of the response in seconds is indicated on the ordinates, the duration of the experiment in minutes on the abscissae.

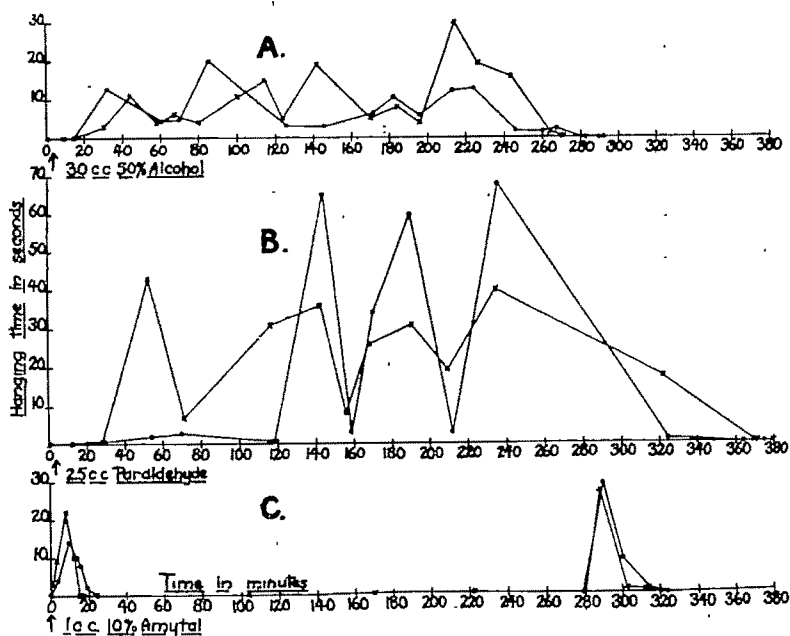


FIG. 2.—Graphs showing the effect of (A) alcohol; (B) paraldehyde, and (C) amytal on the hanging response.

was entirely absent during the sleeping period, lasting four hours, but was present for a short time, first before the animal fell asleep, and again for a while during the waking period.

For purposes of the discussion at hand, the above records will suffice. They all show that the reflex is always present in the state aroused by cerebral depressants. However, these drugs produce wide quantitative variations in effect, which it will be of considerable interest to investigate later.

DISCUSSION.

Since the site of action in the brain is not known for the various drugs used in the above experiments, it is not possible at the present time to determine definitely how these drugs bring out the grasp reflex in adult animals. Some light, however, can be obtained from the following considerations. It has been established through the observations of Janischewsky, Schuster and many others that tumours or other lesions of the frontal lobes in man cause the reflex to appear. As has been frequently suggested, this must mean that under normal conditions the reflex is inhibited by impulses which have their origin in the parts of the brain affected or destroyed by the lesions. The evidence at hand indicates that the reflex mechanism itself must be located fairly far down in the brain-stem, probably in the region of the red nuclei (Minkowski, 1928; Troemner, 1928). The reflex could be brought out, then, either by a lesion or paralysis of a special part of the frontal lobe, or by severance of the connection between these lobes and the reflex centres in the stem. On this basis it may be assumed, for the moment, that the depressants described above paralyse the mechanisms in the frontal lobes, block the pathways from the frontal lobes to the motor centres in the cortex, particularly the occipito-frontal bundle of Schuster and Caspar, or block the pathways from the lobes to the lower centres. That the frontal lobes are involved would seem to be indicated by the fact that the animals are usually stuporous when the reflex is present. That the drugs must attack the nervous system also at a fairly low level is suggested by the observation that the reflex is brought out by hypnotics which are thought to act chiefly on the sleep mechanism in regions around the third ventricle. The results of the experiments with amytal and the other hypnotics are worthy of consideration in this connection, although their significance is not at all clear.

SUMMARY.

(1) The grasp reflex can be brought out in adult monkeys by several pharmacological agents: bulbocapnine, carbon dioxide, ether, chloroform, amytal, paraldehyde, alcohol, luminal, hyoscine, cocaine,

morphine, apomorphine, camphor, insulin, chloral hydrate, eserine, and strychnine.

(2) All of these agents in the large doses given are cerebral depressants and have a definite effect on the responsiveness of the animals, producing a dazed or stuporous condition.

(3) Seven drugs failed to bring out the reflex: adrenalin, atropine, pilocarpine, pituitrin, caffeine, nitroglycerine, and histamine.

(4) All of these drugs in the doses given act as cerebral stimulants, or peripherally, without affecting the central nervous system to any marked degree.

(5) It is suggested that the drugs which bring out the reflex must either paralyse the frontal lobes or block the inhibitory impulses in the pathways from the frontal lobes to motor regions or to the reflex mechanism in the brain-stem.

BIBLIOGRAPHY.

- JANISCHESKY, A. (1928). *Deutsch. Zeitschr. f. Nervenheilkunde*, **102**, 177.
MINKOWSKI, M. (1928). *Handbuch d. biologischen Arbeitsmethoden*, Abt. 5, Physiol. Abt.
RICHTER, C. P. (1931). *Arch. Neurol. and Psychiat.*, **26**, 784.
RICHTER, C. P., and PATERSON, A. S. (1931). *Journ. Pharm. and Exp. Therapy*, **4**, 677.
Idem. (1932). *Arch. Neurol. and Psychiat.* (in press).
SCHUSTER, P., and CASPAR, J. (1930). *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, **129**, 789.
TROMNER, E. (1928). *Journ. Psychol. u. Neurol.*, **35**, 194.
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CATAPLEXY.

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By cataplexy—a term first used by Henneberg—is meant the episodic occurrence of tonelessness, generalized or localized, as a reaction to an emotional stimulus (usually laughter). During the attack there is no impairment of consciousness, the cataplectic attack differing in this respect from the “Lachschlag” of Oppenheim.

Commonly the patient, while laughing heartily, suddenly becomes toneless, as a consequence of which, if standing, he falls, or, if seated, droops forward. Objects are dropped from the hand. The jaw drops, but relaxation of the sphincters rarely occurs. For from several seconds to several minutes the patient cannot move, after which he suddenly regains complete control of his musculature. Less frequently cataplexy is localized, being confined to the jaw or one or more of the extremities.

Emotions other than laughter that have brought on cataplectic attacks are the joy and surprise of unexpectedly meeting an old friend on the street; the excitement of receiving a good hand at cards; the emotion associated with orgasm; the unpleasant emotion of a father about to spank his child. In Holmes' patient attacks occurred when he was startled, as by the sound of a tire bursting or on being silently overtaken by a cyclist.

In some cases there seems to be a relation between the intensity of the emotion and the severity of the cataplexy. Thus, in Case 2, recorded in my recent paper, hearty laughter led to profound tonelessness of the jaw, neck, arms and shoulders, while the mildly unpleasant emotion incident to leaving a warm comfortable bath resulted merely in a slight relaxation of the jaw. Similarly, in Case 3, in the same paper, the patient on hearty laughter was overcome by generalized tonelessness, so that his knees sank, his arms dropped, and his head fell either forward or backward. On the other hand, if, while holding and reading a newspaper, he came across a familiar statement, the resulting mildly pleasurable feeling led merely to a slight hypotonia in the arms, so that

involuntarily he lowered the paper an inch or two; sometimes, on such occasions, without perceptibly lowering the paper, he became aware of a sense of relaxation in his arms.

The literature contains sixteen cases in which the opportunity presented itself to examine the patient *during* the cataplectic attack (Jacobssohn; Gillespie; S. A. K. Wilson, Case 2; Worster-Drought; Stewart; de Villaverde; Ratner, Case 2; Martin; Zehrer, Case 3; Bromberg; Fröderberg; Wagner, Case 1; Serejski and Frumkin, Case 1; Cave, Cases 17 and 24; and Silverstein). In nine instances the muscle tone was noted, being always diminished or absent. Ten authors report on the deep reflexes: eight found them absent or diminished, one found them normal (Fröderberg), and one noted them as present (Bromberg). The response to plantar stimulation was observed in four instances: in two cases it was normal; in Stewart's case the plantar reflexes were "either absent or indefinite"; in Wilson's case there was a "slight but definite" extensor response. The condition of the pupils was noted in eight cases: in two (Ratner; Serejski and Frumkin) they were small and did not react to light; in both of Cave's cases they were noted as small, but no mention was made of their reaction to light; in Martin's case they were dilated and did not react; in the remaining three cases (Gillespie; Wilson; de Villaverde) they reacted to light, but the size was not mentioned.

The overwhelming majority of patients with cataplexy complain also of episodic morbid somnolence—a combination of symptoms to which the term narcolepsy, or Gélinau's syndrome, is applied. According to my count, over 180 cases of Gélinau's syndrome have been recorded. On the other hand, of patients suffering from cataplexy but free of morbid somnolence, only fourteen have been recorded (Symonds; Holmes; S. A. K. Wilson, Case 5, and an unnumbered case on page 95; Rosenthal, Case 7; Rothfeld; Münzer; de Villaverde; Ratner, Cases 4 and 7; Martin; Tsiminakis, Case 1; Wagner, Case 2; and Fouché). Cohen made brief mention of a case of spastic diplegia with cataplectic attacks; nothing was said of morbid somnolence, and one infers that it was absent.

It is my purpose here to record two recently observed cases of "cataplexy only."

REPORT OF CASES.

Case 1.—Coloured girl. Two cataplectic attacks during her 16th year. Subsequently two types of attack occurred: (1) falling attacks occurring independently of emotional stimuli, and (2) attacks of unconsciousness without

convulsions. At 17, tremor of the right arm, later limiting itself to the right hand and present also during sleep developed.

An intelligent coloured girl, aged 17, first came under my notice on July 10, 1930.

Past history.—She had always been frail, having had three attacks of pneumonia during the first six years of life. At 12 she began to complain of intermittent aching of her various joints. At 15 she began to have fleeting precordial pains and dyspnoea. She tired readily. At 16 she began to have intermittent swelling of both ankles, without pain or redness.

At 15 years and 10 months the first menstrual period occurred. The periods were usually six weeks to two months apart. The patient was never aware of sex desire and had never had coitus; in this respect she was unique among her friends.

Cataplexy.—The first neurological symptom was a cataplectic attack occurring several months prior to the first menstrual period. The patient was standing talking to her sister and laughing heartily. In the midst of a sally of laughter she dropped without warning to the floor. On the floor she was able to attain the sitting posture and to move her legs a little, but was unable to get up. There was no disturbance of consciousness, and she neither wet nor soiled herself. She was chagrined over this unheard of type of disability, and her laughter gave way to tears; "I didn't know why I had gotten weak all of a sudden, without any cause—just from laughing." After five minutes the patient was able to get up, and then felt perfectly well.

Six months later another attack occurred, an exact duplicate of the first. No further cataplectic attacks occurred, in spite of the fact that she frequently laughed. On such occasions there was not even a feeling of weakness.

"Falling attacks."—During the six months following the second cataplectic attack (i.e., from June to December, 1929), the patient had twenty or more "falling attacks" occurring independently of emotional experience. They occurred, for example, while she was out walking by herself. Since she worked long hours in a hair-dressing establishment, standing most of the time on her feet, she was inclined to attribute the attacks to fatigue.

Attacks of unconsciousness.—In the autumn of 1929 the patient began to have infrequent attacks of unconsciousness, unassociated with self-injury, convulsions, biting of the tongue, or relaxation of the sphincters. At first these occurred only at her place of employment, and she ascribed them to the heat of the hair-drying machine near which she worked. In May, 1930, two attacks occurred under altogether different circumstances. (1) One Sunday morning, in church, while walking down the aisle to her seat, she suddenly fell unconscious, remaining so for several minutes. (2) A few weeks later, again at a church service, a quarrel arose between the pastor and one of the members of the congregation. Presently the latter advanced menacingly down the centre aisle to the pulpit, and great excitement spread through the congregation. The effect of this was to make the patient feel "nervous and shaky," and she decided to leave. Inasmuch as she was sitting in the front row of the

balcony, she had to ascend about ten steps to reach the aisle leading to the exit. On the third or fourth step she fainted, regaining consciousness in the accident ward of a nearby hospital.

Subsequent to December, 1929, the patient had no further "falling attacks," and but two attacks of unconsciousness (these being the two in church).

"*Nervous breakdown.*"—On January 1, 1930, the patient had a "nervous breakdown." Having been out very late the night before, she took a fifteen-minute nap in the early evening, from which she awakened feeling "really sick: my heart was paining, I couldn't get my breath; my heart felt to me as if it was coming out of my body. I was shaking all over. I felt nervous and wept." In an hour the generalized tremor subsided, but there remained a tremor of the right arm that persisted for six weeks. For a time this was so marked that she was unable to feed herself with the right hand. The tremor of the right arm was replaced by a tremor of the right hand, which was still present when I saw the patient.

Upon careful questioning it was ascertained that there was no history of morbid sleepiness.

Physical examination.—The patient was slender, being 63 in. (160 cm.) tall, and weighing 108 lb. (49 kg.). The right lobe of the thyroid was slightly enlarged. The heart was not enlarged. There was a loud systolic murmur. The pulse-rate varied from 80 to 90. The blood-pressure was 146 systolic, and 70 diastolic.

The right arm was slightly weaker than the left. There was a marked tremor of the right hand, present even when the hand was at rest. Her relatives observed that it was also present during sleep. There was a faint, almost imperceptible tremor of the outstretched fingers of the left hand. The finger-nose test showed moderate ataxia, more so on the right. Alterations of tone were not apparent on passive motion. The results of the examination were otherwise without significance.

Laboratory examinations.—The blood-counts were normal. The Wassermann reaction of the blood and spinal fluid and the colloidal gold curve were negative (other spinal fluid examinations were not made). The basal metabolic rate on two occasions was minus 4 per cent. and plus 6 per cent. A roentgenogram showed a normal sella turcica.

To summarize, the patient presented three groups of symptoms: (1) Rheumatic-arthritic-cardiac symptoms: joint pains for the past five years; fatigue, dyspnoea and precordial pains for the past two years; swelling of the ankles for the past year; signs of mitral insufficiency. (2) Evidence suggestive of gonadal inadequacy; delayed puberty and deficient libido. (3) Nervous symptoms: a cataplectic attack one and a half years ago, followed by a similar attack six months later; during the ensuing six months, over a score of "falling attacks" occurring independently of emotional stimuli; during the past nine months a

number of attacks of unconsciousness, one of which occurred during an exciting episode in church; a "nervous breakdown" six months ago, characterized by an episode of acute anxiety and generalized tremor, leaving in its wake a tremor of the right arm lasting six weeks, which was in turn succeeded by a tremor of the right hand. At present marked tremor of the right hand (present also during sleep); an almost imperceptible tremor of the fingers of the left hand; slight weakness of the right arm; no disturbances of tonus. The patient was under my observation for several months, during which the tremor of the right hand remained unchanged. The only treatment consisted of the oral administration of potassium iodide. I lost sight of her when she moved to another city.

Comment.—The interest in this case lies in the evidence pointing to the possibility of a striatal lesion—a virtually unilateral tremor, present also during sleep. This possibility is enhanced by the presence of rheumatic cardiac disease, since there is increasing acceptance of the view that the chorea often associated with rheumatic disease is dependent on a lesion of the striatum [7]. At the same time the evidence of striatal disease in the present case is far from conclusive, since (except during the two attacks of cataplexy) changes in tonus were absent.

Evidence suggesting the possibility of a striatal lesion in a patient with cataplexy is of more than usual interest. Several authors have suggested in recent years that the striatum might play a role in the production of cataplexy. Thus, Redlich emphasizes the tone-regulating function of the striatum, pointing out that in destructive striatal lesions there is interference with the tone-inhibiting centres, resulting in hypertonia. He suggests that an opposite process occurs during lively emotions, leading in extreme instances to the hypotonia of cataplexy. He confesses that the matter is still unsettled, but he feels that the process is functional rather than anatomical; he speaks of it as "a disturbance of the equilibrium of the subcortical centres."

Rothfeld has made a noteworthy suggestion based on the assumption that the tone-inhibitory globus pallidus is itself normally inhibited by the neostriatum, and that both of these structures are capable of being inhibited by the thalamus. He contrasts the external manifestations of sad and gay emotions: a man following a hearse is bowed down with grief, his face is rigid, and there is paucity of associated arm movements on walking—an akinetic-hypertonic picture; on the other hand, a lad following a military band carries himself erect, swings his arms briskly, and displays lively facial mimicry—a hyperkinetic-hypotonic picture.

The hypotonic phenomena associated with happy emotions are even more conspicuous in laughing children, who have not yet learned to inhibit the free expression of their moods. The akinetic-hypertonic (sad) picture is regarded by Rothfeld as a manifestation of inactivity of the tone-inhibitory pallidum; the hyperkinetic-hypotonic (happy) picture suggests, on the other hand, a temporary suspension of the pallidum-inhibitory function of the neostriatum, as a result of which the pallidum is for the moment permitted to function without restriction. Rothfeld therefore proposes that laughter be defined as a reaction which occurs when cheerful stimuli "affect the subcortical ganglia in such a way that the thalamus releases inhibitory impulses which restrict the regulative effect of the neostriatum on the pallidum." Under suitable conditions this process may be exaggerated to the point where tonelessness, i.e., cataplexy, results.

We still know too little about the striatum to be dogmatic. Nevertheless, the relative frequency of Gélineau's syndrome in patients with the Parkinsonism of epidemic encephalitis lends probability to the assumption that the striatum is in some way involved in the mechanism of cataplexy. This probability is enhanced, if only slightly, by the case here reported. It is well to remember that so far there has been no necropsy in a patient with cataplexy.

While ordinarily Gélineau's syndrome and epilepsy occur separately, there are occasional cases containing features of both. Thus Grainger Stewart's patient was an epileptic who later developed cataplectic attacks and, still later, sleep attacks. Conversely, Holmes' patient, who had cataplexy but no sleep attacks, later developed epilepsy. In view of this occasional association it is noteworthy that our patient had attacks of unconsciousness, though without convulsions. The continuous tremor of her hand is similar to a phenomenon described by Kojevnikov under the name *epilepsia partialis continua*: continuous muscular twitchings occurring in any part of the body, without impairment of consciousness, in the intervals between major epileptic attacks [28].

A lesser point of interest is that our patient is coloured. But two other cases of negroes with cataplexy have been reported, both of them being cases of Gélineau's syndrome (Thrash and Massee; Wahl).

Case 2.—White male, of a manic-depressive disposition. Manic attacks at 16 and at 18. Beginning at 15 or 16, attacks of cataplexy localized in the right arm and hand. Beginning at 18, attacks of unconsciousness apparently of an epileptic nature.

An intelligent young white man began at 14 to have wide variations of

mood, alternating between gloominess and exhilaration. At 16 he had a manic excitement, lasting three or four months. He made a good recovery. At 18 he had a second manic attack, lasting two weeks. During the second week of this attack, on August 25, 1931, he was admitted to the Harrisburg State Hospital. Five days after admission the attack subsided, and thereafter he showed no further mental symptoms.

Cataplexy.—The patient was "high-strung" and trembled when under tension, e.g., when presented to the medical staff. In discussing this difficulty he revealed that for two or three years he had been having attacks of inadequate control of his right arm and hand. (He was right-handed in everything he did.) Frequently these attacks were precipitated by excitement. For example: (1) It frequently happened that in the midst of an exciting volley at tennis his racquet dropped from his hand; in less extreme instances he was able to hold on to the racquet, but it wobbled to such an extent that he was unable to play the ball accurately. (2) On several occasions, while playing an exciting game of cards, he suddenly lost control of his right hand in which he was holding the cards, with the result that "I sort of sprawled the cards." (3) An instructive episode occurred at the age of 15 or 16. The patient was employed as an errand boy in a grocery store. One morning, returning from having delivered several orders, he turned his money over to his employer (a woman). She called his attention to the fact that he was ninety-six cents short. As an old friend of his family, she knew him well and did not question his honesty; she felt rather that he had erred in giving change to one of the customers. The patient was painfully embarrassed. Ten minutes later she gave him another order to deliver. He placed the basket on his right arm and started to leave "As I was about to open the door, my right arm shook and brought the basket down to my wrist." The attack was sufficiently brief to permit him to recover the basket with his right hand.

Less frequently the symptom occurred in situations free of excitement. For example: (1) While he was writing the fountain-pen occasionally slipped from his hand. Sometimes, without dropping the pen, he found himself momentarily unable to guide it properly. (2) During his convalescence at the hospital he noted on several occasions, while drinking coffee at breakfast, that his right arm trembled. On three occasions this was so severe that some coffee was spilt, but the cup was never dropped.

An invariable characteristic of the attacks was that they lasted but a few seconds and were not accompanied by disturbance of consciousness. As regards the tone of the arm during the attack, the patient stressed the fact that his arm was "weak"; it never "drew up," nor did he use any of the other terms used by laymen in describing a Jacksonian fit. The phenomenon never occurred during laughter. It never involved any part of the body other than the right arm and hand.

The patient never suffered from morbid somnolence.

Examination.—The patient was well developed. The examination showed no abnormalities, save a moderate tremor of the tongue and outstretched fingers.

Attack of unconsciousness.—On October 27, 1931, for the first time in his life, the patient fell unconscious. He was sitting in the day-room of the ward, playing checkers with a fellow-patient. Without warning he lost consciousness and was laid on the floor, where he lay quietly for twenty minutes before coming to himself. There were no convulsions, nor were the bladder and bowels evacuated. No physician saw him at the time.

The patient was given parole on November 5, 1931. During the ensuing five months he had four attacks of unconsciousness, in some of which he showed definite tonic and clonic spasms. He had numerous attacks of cataplexy.

Comment.—The limitation of the cataplexy to the arm and hand is noteworthy.

Since patients with cataplexy react unfavourably to strong emotional stimuli, the circumstances surrounding the onset of the second manic attack are remarkable. The patient and an uncle went on a ten-day motor tour. On the way home the uncle provided himself with a large quantity of strong liquor, which he consumed freely. Since the patient does not drive, he was forced to entrust himself to his intoxicated uncle, and throughout the remainder of the trip he was filled with dread. The manic attack began while he was in this state of mind; on reaching home he was already over-talkative and elated.

In view of the occasional association, already alluded to, of the phenomena of epilepsy and those of Gélinau's syndrome, the attacks of unconsciousness are noteworthy. For the same reason, the family history is significant. The father, a civil engineer, a robust man of unusual intelligence, began at 17 to have *petit mal* attacks. From 17 to 20 he took a difficult course at a German technical school. During this period he was under great strain, and the attacks were frequent. Graduation at 20 was accompanied by a sense of profound relief. Thereafter the attacks occurred but infrequently. He never had a *grand mal* attack or a cataplectic attack. A paternal great-aunt and a maternal uncle had major epilepsy.

SUMMARY.

Two cases of cataplexy are presented. Neither patient had morbid somnolence. In addition to cataplexy, both patients had attacks of unconsciousness. The first patient had a constant unilateral tremor, present also during sleep, suggesting the possibility of a lesion of the corpus striatum.

REFERENCES.

- [1] BROMBERG, W. "Narcolepsy associated with Chronic Encephalitis," *Arch. Neurol. and Psychiatr.*, 1930, **24**, 194.
- [2] CAVE, H. A. "Narcolepsy," *ibid.*, 1931, **26**, 50.
- [3] COHEN, H. *Brain*, 1928, **51**, 127.
- [4] FOUCHÉ, O. H. "Cataplexy," *Proc. Roy. Soc. Med.*, 1931, **24**, 318.
- [5] FRODERBERG, H. "Ett fall av narkolepsi med kataplexi," *Hygieia* (Stockholm), 1930, **92**, 788. Abstracted in *Zentralbl. f. d. ges. Neurol. u. Psych.*, 1931, **59**, 467.
- [6] GILLESPIE, R. D. "A Case of Cataplexy," *Journ. Neurol. and Psychopath.*, 1927, **8**, 83.
- [7] GREENFIELD, J. G., and WOLFSOHN, J. M. "The Pathology of Sydenham's Chorea," *Lancet*, 1922, **2**, 603.
- [8] HENNEBERG, H. "Ueber genuine Narkolepsie," *Neurol. Zentralbl.*, 1916, **35**, 282.
- [9] HOLMES, G. "A Case of Falling on Noise and Surprise," *Brain*, 1927, **50**, 720.
- [10] JACOBSSOHN, E. "Ueber die Einwirkung multipler Sklerose auf Narkolepsie," *Klin. Wochenschr.*, 1927, **6**, 1241.
- [11] LEVIN, M. "Narcolepsy (Göllneau's Syndrome) and Other Varieties of Morbid Somnolence," *Arch. Neurol. and Psychiatr.*, 1929, **22**, 1172.
- [12] MARTIN, J. P. "Narcolepsy with Cataplectic Attacks," *Proc. Roy. Soc. Med.*, 1929, **22**, 598.
- [13] MUNZER, F. T. "Ueber das Vorkommen von isoliertem 'affektivem Tonusverlust,'" *Med. Klin.*, **24**.
- [14] OPPENHEIM, H. "Ueber Lachschlag (Lach-Schwindel—Lach-Ohnmacht)," *Monatschr. f. Psychiatr. u. Neurol.*, 1902, **11**, 241.
- [15] RATNER, J. "Zur Lehre der Diencephalosen (Beiträge zur Narko- resp. Pynolepsiefrage)," *Arch. f. Psychiatr. u. Nerv.*, 1928-29, **86**, 524.
- [16] REDLICH, E. "Ueber Narkolepsie," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1925, **95**, 256.
- [17] ROSENTHAL, C. "Ueber die krankhaften Dissoziationszustände bei der echten Narkolepsie und dem verzögerten psychomotorischen Erwachen (Wachanfälle)," *Arch. f. Psychiatr.*, 1928, **84**, 120.
- [18] ROTHFELD, J. "Affektiver Tonus- und Bewusstseinsverlust beim Lachen und Orgasmus (Gelo- und Orgasmoepsia)," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1928, **115**, 516.
- [19] SEREJSKI, M., and FRUMKIN, I. "Narkolepsie und Epilepsie," *ibid.*, 1930, **123**, 238.
- [20] SILVERSTEIN, A. "A Case of Göllneau's Syndrome," *Arch. Neurol. and Psychiatr.*, 1931, **25**, 1876.
- [21] STEWART, GRAINGER. *Brain*, 1928, **51**, 126.
- [22] SYMONDS, C. P. "Narcolepsy as a Symptom of Encephalitis Lethargica," *Lancet*, 1926, **2**, 1214.
- [23] THRASH, H. O., and MASSEY, J. C. "Narcolepsy," *Journ. Amer. Med. Assoc.*, 1928, **91**, 1802.
- [24] TRIMINAKIS, K. "Zur Frage der Narkolepsie," *Wien. klin. Wochenschr.*, 1930, **43**, 1147.
- [25] DE VILLAVARDE, J. M. "Ueber einige Eigentümlichkeiten der Narkolepsie," *Arch. f. Psychiatr.*, 1928-29, **86**, 129.
- [26] WAGNER, O. P. "Comment on the Mechanism of Narcolepsy," *Journ. Nerv. and Ment. Dis.*, 1930, **72**, 405.
- [27] WAHL, E. F. "Narcolepsy," *Southern Med. Journ.*, 1931, **24**, 169.
- [28] WILSON, G., and WINKELMAN, N. W. "Partial Continuous Epilepsy," *Arch. Neurol. and Psychiatr.*, 1924, **11**, 530.
- [29] WILSON, S. A. K. "The Narcolepsies," *Brain*, 1928, **51**, 63.
- [30] WORSTER-DROUGHT. *ibid.*, 1928, **51**, 126.
- [31] ZIEHLER, H. "Zur Klinik der Narkolepsie," *Allgem. Zeitschr. f. Psychiatr.*, 1929, **92**, 268.

THE STRUCTURE AND CONNECTIONS OF THE THALAMUS.¹

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JUST over twenty years ago, in the Arris and Gale lectures which he delivered on the subject of the evolution of the cerebral hemispheres, Elliot-Smith [16] expressed his opinion that the key to the interpretation of the structure of the rich cortical component of the cerebral hemispheres which is found in mammals—the neopallium—lies in an intensive study of the thalamus. For it is well known that, with the solitary exception of olfactory impulses, all sensory impulses which are destined to reach the cerebral cortex have first to be filtered through the mass of grey matter which is found in the walls of the third ventricle, the optic thalamus. From the thalamus such sensory impulses are projected on to the cortex by thalamo-cortical fibres, and their mode of distribution to topographical cortical areas is no doubt determined in large part by the spatial relationship of the thalamic nuclei from which these fibres arise. This fundamental fact has been emphasized by several anatomists (von Monakow [43], Cajal [5], Elliot Smith [16]), and rests on the observation that projection fibres usually take the most direct and shortest route from the thalamic centres to the cortex. Not only does the thalamus in this way determine a spatial localization in the cortex, but it is possible for sensory impulses on their way through the thalamus to undergo modification and selection as the result of being brought into relation with the activities of intrinsic thalamic mechanisms. In other words, the neopallium must depend entirely on the thalamus for the precise nature of the sensory material which it receives indirectly from peripheral receptors. It is true that there is evidence to indicate that cortical mechanisms can modify thalamic activities by inhibitory influences, but the fact remains that, so far as the purely sensory functions of the neopallium are concerned, the latter from the developmental and functional point of view is to be regarded as a dependency of the thalamus and not *vice versa*. This

¹ The material of this paper formed the basis of two Arris and Gale lectures delivered at the Royal College of Surgeons on February 17 and 19, 1932.

consideration further emphasizes the necessity of a sound knowledge of intrathalamic connections before it is possible to gain a fuller appreciation of the part played by the highest functional levels of the brain in the working of the mind.

But the thalamus is much more than a relay station for the passage of sensory impulses on their way to the cerebral cortex. Into the thalamus there come fibres conveying sensory impulses of every possible kind, somatic and visceral, impulses which convey intimation of changes within the organism itself and of changes in the external environment. Here, long before the neopallium has appeared in evolutionary history, a mechanism is provided for the interaction and blending of these diverse afferent impulses, and, in relation to this plain anatomical fact, it may be noted that there is accumulating evidence based on clinical and psychopathological observation that the thalamus is the anatomical equivalent of the very threshold of consciousness.

Thus it is clear that a study of thalamic structure and function is of the highest importance in connection with fundamental problems of neurology and of normal and abnormal psychology.

It is curious that less should be known of the intrinsic structure and connections of the thalamus than perhaps of any other part of the brain. While a great deal of attention has been focused on the cerebral hemispheres above and the brain-stem below, the "Zwischenhirn" or between brain, which forms such an essential link between the two, has only comparatively lately begun to be submitted to a really intensive scrutiny. There are two main reasons for this neglect of thalamic anatomy. One is the confusion of nomenclature and the lack of definition which occur in the literature of the subject, and which have repeatedly led to misconceptions and misinterpretations which it has been impossible to harmonize with one another, and the other is the difficulty of applying the usual experimental methods to this part of the brain. It is clear, however, that the experimental method can be of little avail without a satisfactory definition of the elements which are to be subjected to study and, indeed, much of what little experimental work has hitherto been done on the thalamus has been vitiated by the neglect of a preliminary and detailed anatomical study. One of the main objects of this paper is to clear the terminological atmosphere so as to provide a sound anatomical basis for future investigations on the thalamic functions.

The thalamus in higher mammals becomes such a complicated structure that it is well-nigh impossible to unravel its complexities by direct anatomical methods. It is essential, in order to define the funda-

mental elements of its composition, to study it in the more simple form in which it is found in small and generalized mammalian types. Then, by a study of a closely graded series of mammalian brains from a comparative anatomical point of view, arranged to correspond as nearly as may be to a true phylogenetic series, it is possible by direct comparison to trace the changes which occur in the development of the more complex from the more simple type of thalamus, and to establish satisfactory homologies of its component parts. Thus, for instance, the nuclear elements of the thalamus of lower mammals may, in this manner, be indirectly compared with those of the human brain, and the way prepared for a satisfactory correlation of clinical observations with the results of physiological experimentation. To institute a comparison between the thalamus of man and the thalamus of a specialized mammalian type such as the dog or cat, without reference to intermediate forms, may lead to fallacious interpretations.

This method of comparative anatomy is a necessary preliminary to any detailed study of the thalamus. As regards the experimental approach, although the method of tracing degenerated fibres by Marchi staining has been applied by several investigators to the study of extrinsic and intrinsic thalamic connections, it has hitherto led to comparatively meagre and uncertain conclusions, partly due to the lack of a precise anatomical study of normal material, but partly due to the fact that the initial lesions have usually not been sufficiently circumscribed. Judiciously used, the Marchi method promises to supply much information. The interpretation of its results so far as it has hitherto been applied to the thalamus has been rendered often difficult because the severity of the lesion has introduced complicating factors. Much of the current anatomical description of thalamic connections is based on degeneration after severe lesions of the brain, and for this reason should be regarded very critically. It is essential to be content with the production of very small and localized lesions, and to make a complete series of serial sections of the material in order accurately to delimit the extent of the lesion and to trace degenerating fibres in continuity to their termination. The greatest care must also be used to distinguish between fibres of passage and those which are directly connected with thalamic nuclei. Large numbers of such records are required and only by prolonged and tedious research will it be possible to complete a survey of the thalamus in this way.

References are made in the course of this paper to some experimental work which the author has carried out on the thalamic connections in

the rat's brain. A detailed account of this study will be found elsewhere [12].

THE GENERAL TERMINOLOGY OF THE DIENCEPHALON.

There is much lack of agreement regarding the terminology even of the main parts of the diencephalon. That which will be adopted here may conveniently be indicated by referring to the diencephalon of the human brain as it appears during the third month of foetal development.

Viewed from the ventricular aspect the lateral wall of the third ventricle shows a relatively large rounded swelling which represents the thalamus *sensu stricto*. Below the thalamic eminence is a well-defined groove called the sulcus hypothalamicus which extends forwards from the region of the aqueduct of Sylvius to the optic recess. This sulcus, it has been suggested, represents the anterior prolongation of the sulcus limitans of the embryonic neural tube which separates the sensory lamina from the motor lamina. This, however, is too doubtful to form the basis of any inferences regarding the functional level of those parts of the diencephalon which lie in relation to it. The more recent embryological studies indicate, indeed, that the basal lamina does not extend further forward than the mid-brain. The hypothalamic sulcus, however, serves to mark the division of the diencephalon into two main parts, the significance of which it is important to recognize. Above the level of the sulcus is the *pars dorsalis diencephali* which consists of the thalamus proper and, above this, the epithalamus. Below the sulcus is the *pars ventralis diencephali* which consists of the hypothalamus and the subthalamus. The epithalamus is represented by the pineal diverticulum from the roof of the ventricle and an elongated swelling which stretches back from the region of the interventricular foramen to the base of the diverticulum. This swelling indicates the position of developing groups of nerve-cells and fibre systems which are intimately related to the olfactory parts of the cerebrum and which, on the basis of comparative anatomy, appear to arise primarily in connection with the pineal organ or epiphysis. The thalamus forms by far the greater part of the *pars dorsalis diencephali* except in the most primitive vertebrates, and it is to be regarded as a great sensory ganglion which receives all varieties of somatic sensory impulses. In higher forms it represents an essential link on the afferent side between the neopallium and lower levels of the central nervous system. The geniculate bodies (which receive terminals of the auditory and visual tracts) are sometimes separated descriptively from the thalamus proper and grouped together

as the metathalamus. This term, however, seems superfluous, for the geniculate bodies are both outgrowths from the main sensory nucleus of the thalamus.

The hypothalamus consists of a glandular outgrowth from the floor of the third ventricle (the pars nervosa of the pituitary gland) and a series of nuclear masses which develop in topographical and functional relation to it. In this region the optic chiasma is situated and, with certain other decussations, becomes included as a part of the hypothalamus. Lateral to the hypothalamus, and not extending medially as far as the ventricular wall, is the subthalamus, which may be regarded broadly as the pathway of all the elements of the lateral fore-brain bundle which pass from the cerebral hemispheres to lower levels and link up the cortex and basal ganglia with the brain-stem and spinal cord. It is bounded medially by the hypothalamus, above by the thalamus proper and the termination of the medial fillet, and its ventro-lateral margin is formed by the cerebral peduncle or *pes pedunculi*. Among the fibre tracts which pervade it are a series of nuclear masses (such as the entopeduncular nucleus, the subthalamic nucleus of Luys, the diffuse cell groups of the *zona incerta*) which form links in a broken chain of nuclear structures connecting up the corpus striatum above with the grey matter in the tegmental region of the mid-brain below (e.g., the red nucleus, substantia nigra, reticular nuclei). The nuclei of the subthalamus form in large part a series of relay stations for fibres which descend from the striatum, and constitute essential elements in the so-called extra-pyramidal motor system. They are also intimately related to the elements of the hypothalamus medially by fibre connections, and there is no doubt that they receive the terminations of certain afferent paths.

This nomenclature of the main parts of the diencephalon is not in accord with that adopted by American neurologists in general (e.g., Herrick [25] and Huber and Crosby [31]), who call the subthalamus the "ventral thalamus," while the term "dorsal thalamus" is reserved for the thalamus proper.

EVOLUTION OF THE THALAMUS:

The relations and general significance of the main subdivisions of the diencephalon may conveniently be indicated by referring to its evolutionary history. The evolutionary development of the diencephalon throughout the vertebrate series is manifested by a progressive elaboration of its dorsal part, and this is apparently contingent at first upon

the termination of an increasing number of direct and indirect sensory paths in it and, later, upon the reciprocal relation which develops between the thalamus and the superposed neopallium. Thus when the diencephalon is followed through a descending series of vertebrates the thalamus proper shrinks, while the epithalamus and the hypothalamus become increasingly important elements respectively. In the most primitive vertebrates, the cyclostomes [26, 27, 56], the thalamus is little more than a slender band of nervous tissue running dorso-ventrally and linking up the epithalamus above with the hypothalamus below. The afferent paths which reach it from the brain-stem and spinal cord without being relayed through the tectum are so small that we are led to the conception of a protean type of vertebrate brain in which somatic impulses reach the diencephalon entirely through tectal connections. Such a type of brain is represented in the accompanying diagram (fig. 1A). The epithalamus comprises the pineal organ and a mass of nerve-cells at the site of its attachment to the roof of the third ventricle, the habenular ganglion, or habenula. The hypothalamus forms a conspicuous swelling in the floor and lower part of the lateral wall of the ventricle and lies in direct relation to the pituitary gland. Both the habenula and the hypothalamus receive rich contributions of fibres from the telencephalon, which is entirely olfactory in function.

It is convenient to draw attention at this point to a distinction in anatomical connections between the dorsal part of the diencephalon and the hypothalamus which seems to imply a fundamental functional contrast. The *pars dorsalis diencephali* (represented in the cyclostome brain practically entirely by the epithalamus and in higher forms incorporating the thalamus proper) is a sensory correlation station which receives impulses of a somatic nature, that is to say, impulses which are the result of stimuli produced directly by changes in the external environment, and through which motor reactions to these stimuli are ultimately rendered possible. In primitive vertebrates there are tecto-habenular connections by which visual and general sensory impulses, &c., are enabled to reach the habenula, and among its cells terminate the fibres of the pineal nerve which also certainly convey exteroceptive impulses, probably of a visual nature. The habenular ganglion thus provides a neural mechanism through which the organism may become aware of the varying conditions of its external environment and by which it can adjust its own behaviour so as best to adapt itself to these conditions. Such exteroceptive functions are essentially connected with the dorsal part of the diencephalon in all vertebrates.

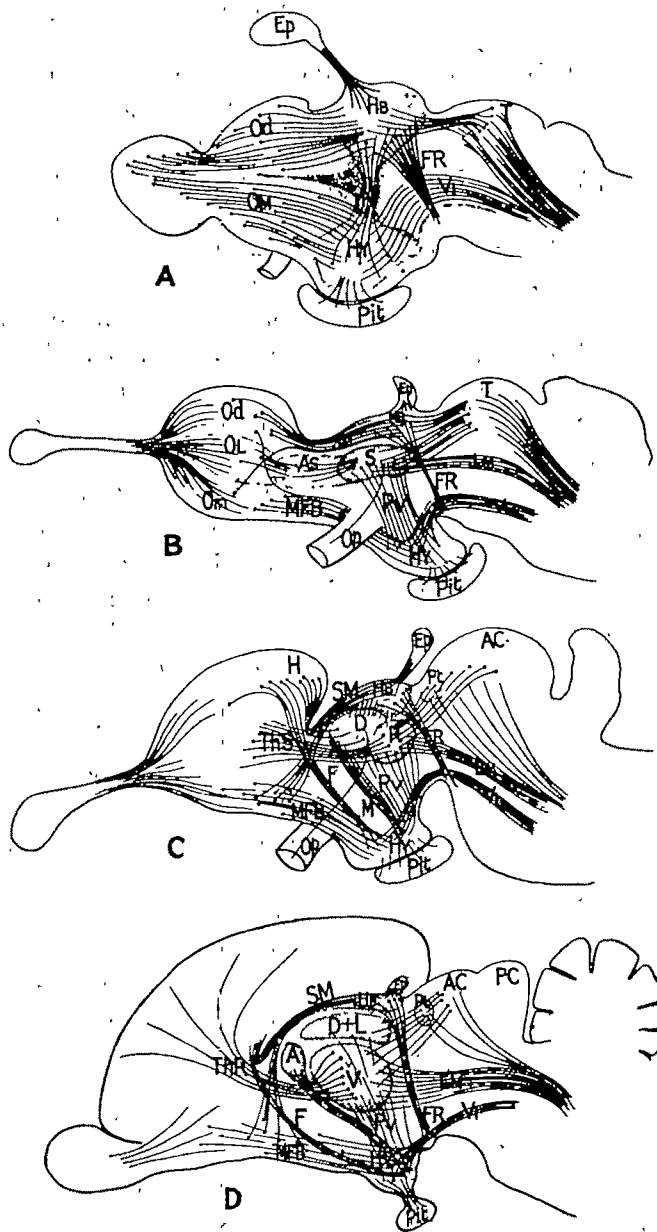


FIG. 1.—Diagrams representing stages in the evolution of the thalamus. *A*. Primitive cyclostome. *B*. Fish. *C*. Reptile. *D*. Mammal. *AC*. Anterior colliculus. *As*. Area somatica. *D*. Nucleus dorso-lateralis anterior. *D + L*. Nucleus dorso-medialis + nucleus lateralis. *Ep*. Epiphysis. *F*. Fornix. *FR*. Fasciculus retroflexus. *H*. Hippocampal formation. *Hb*. Habenula. *Hy*. Hypothalamus. *LM*. Medial lemniscus. *M*. Mammillo-thalamic tract. *MFB*. Medial forebrain bundle. *Od*. Area olfactoria dorsalis. *Ol*. Area olfactoria lateralis. *Om*. Area olfactoria medialis. *Op*. Optic tract. *PC*. Posterior colliculus. *Pit*. Pituitary. *Pt*. Pretectal nucleus. *Pv*. Periventricular system. *R*. Nucleus rotundus. *S*. Main sensory nucleus of the thalamus. *SM*. Stria medullaris. *T*. Tectum. *ThR*. Thalamic radiations. *ThS*. Thalamo-striate fibres. *V*. Ventral nucleus. *Vt*. Ascending visceral tracts.

The hypothalamus, on the other hand, is a visceral correlation centre. In it there terminate fibres which arise from visceral nuclei in the brain-stem. This fact has been demonstrated by direct anatomical methods in the case of lower vertebrates in which the ascending visceral tracts are relatively conspicuous [34]. In higher vertebrates and man, the intimate relation between the hypothalamus and visceral centres has been corroborated by experimental and clinical evidence. This evidence indicates that the hypothalamus comprises a neural apparatus through which are controlled and regulated vegetative functions of the organism as represented by fundamental metabolic processes, endocrine activity, visceromotor mechanisms, vasomotor phenomena, &c. From this it may be inferred that the hypothalamus in mammals is certainly connected directly or indirectly with viscerosensory nuclei in lower levels of the central nervous system as in lower vertebrates, and there is some anatomical evidence to confirm this proposition. The close relation between the hypothalamus and the pituitary gland has already been mentioned. That the two work together in the closest collaboration to form a unified neuroglandular mechanism is proved by anatomical and physiological observation. Some of the nuclei of the hypothalamus are directly related by nerve-fibres to both the anterior and posterior lobes of the pituitary, and the intimate vascular connections between the hypothalamus and the gland have recently been emphasized by the work of Popa and Fielding [49] who, working in Elliot Smith's laboratory, have described a portal circulation in the region of the tuber cinereum. In view of the part which the pituitary is known to play in controlling growth in foetal and post-natal life, its dominating influence over the endocrine system generally, its power of regulating fundamental rhythms of sexual life and development, &c., it is not unreasonable to suppose that through its connections with the gland the hypothalamus provides a region of the brain in which the basic vital activities of the organism may be echoed in terms of neurogenic processes. These considerations lead to the suggestion that the hypothalamus is the recipient of those vague and undefinable impressions which arise in association with all sorts of visceral activities and metabolic processes, and which, in their totality, represent sensory material by which the organism is enabled to appreciate itself as a unified being, an individual existing as an organised entity, without special reference to the external environment. In general, then, the hypothalamus may be regarded as a part of the diencephalon which, by its nervous connections and through the direct liaison which it establishes with the hormonal regulatory system *via* the

pituitary, mediates the integration of visceral impulses and plays an essential part in the control of the internal milieu of the organism. Thus it stands in direct contrast to the functional implications of the dorsal part of the diencephalon. While the latter is the recipient of impulses on the basis of which the organism may develop an awareness of its external milieu and adapt its overt behaviour accordingly, the former is the recipient of impulses on the basis of which the organism may develop an awareness of its internal organic activities and through which sensory experiences are endowed with an affective tone.

In all vertebrates, the dorsal part of the diencephalon and the hypothalamus are linked together by a strand of cells and fibres which form what may be called the periventricular system. In the cyclostome brain this primitive connecting link is apparent as a narrow band lying vertically in the lateral wall of the third ventricle and connecting the habenula with the hypothalamus. Through this periventricular system the somatic correlation centres of the diencephalon are brought into functional relation with the visceral correlation centres. This provides a basic mechanism whereby the organism is enabled to equate consistently the impressions which it derives from the outside world with the organic functions of its own being.

In cyclostomes the whole diencephalon receives rich fibre connections from the olfactory centres of the cerebral hemispheres. Both the epithalamus and the hypothalamus, indeed, are directly continuous with the dorsal and medial olfactory areas without any clear line of demarcation.

In the brain of fishes (fig. 1 *B*), in association with an increasing proportion of somatic impulses entering the dorsal part of the diencephalon, the thalamus proper shows signs of incipient differentiation immediately below the epithalamus (Herrick [26]). In this way arises a part of the diencephalon which is not under the direct influence of olfactory impressions. It is said by some authorities that in certain teleostean types at least it is possible to trace a few olfactory fibres directly into the thalamus proper, but, if this is so, they are insignificant and rapidly disappear in the process of further evolutionary development. The thalamus receives its somatic impulses mainly through the tectum, but there is the beginning of a lemniscus system of sensory tracts from lower levels, and collaterals of the optic tract also terminate in it (as they also do even in cyclostomes according to Tretjakoff [56]). The thalamus is also beginning to push its influence forwards into the sphere of the telencephalon—to invade a territory

which was primarily a domain of the olfactory system. Here it leads to a differentiation of a region which has been called the area somatica and which is continuous anteriorly with the lateral olfactory area of the fore-brain. The area somatica is the precursor of the somatic part of the corpus striatum of higher forms. In fishes there is no clear boundary between the diencephalon and the telencephalon so far as intrinsic structure is concerned. The whole fore-brain can, indeed, be described as consisting of three longitudinal columns of cells of which the dorsal is represented by the dorsal olfactory area (precursor of the hippocampal formation) prolonged back without interruption into the epithalamus, the ventral by the medial olfactory area (precursor of the septal and parolfactory areas) and the hypothalamus, while between the two is another column comprising the lateral olfactory area, the area somatica and the thalamus proper. The fibre connections between the thalamus and the area somatica of the hemisphere represent the forerunners of the strio-thalamic and thalamo-striate connections. It will be noted in the diagram that the dorsal olfactory area becomes related by efferent connections with the hypothalamus, and this marks the appearance of a fornix system which is first seen in the selachian brain. The medial olfactory area also sends fibres dorsally to the epithalamus, representing the olfacto-habenular component of the stria medullaris.

In the reptilian brain (fig. 1 C), a pronounced elaboration of the *pars dorsalis diencephali* may be observed (De Lange [36] and Crosby [30]). The thalamus proper has increased considerably in size and shows an intrinsic differentiation into fairly well-defined nuclear masses. Several thalamic nuclei have been described, but here attention may be especially directed to the two which make up the bulk of the somatic part of the thalamus, the nucleus dorso-lateralis anterior, and the nucleus rotundus. Both these are composed of similar types of cells and are not everywhere clearly separated from each other. Both are connected with somatic areas in the lateral part of the cerebral hemisphere. They receive afferent impulses through tectal connections, and the nucleus rotundus, at least, is believed to receive lemniscal fibres. Together they represent the main somatic sensory centre of the diencephalon, equivalent to the "*pars dorsalis diencephali*" of amphibia as defined by Herrick [25], and to the ventral group of nuclei, the main part of the nucleus anterior, the dorsal nucleus of the lateral geniculate body and probably the medial geniculate body of mammalia (*vide infra*, p. 433). The nucleus rotundus is a very distinctive element in the sauropsidan thalamus. That it represents a part of the ventral group of nuclei of the mammalian

thalamus (possibly the nucleus medialis ventralis) is almost certain. It is equally certain, however, that its size and marked differentiation is a sauropsidan specialization associated with the relatively immense size of the striatum in reptiles and birds. The rich strio-thalamic connections form a thick bundle of fibres which sweep round and encircle the nucleus, delimiting it very sharply from neighbouring elements. It is thus unreasonable to expect that its homologue in the mammalian thalamus will necessarily resemble it in shape and proportions, as the relative development of the striatum is very different. It is necessary to mention this point as attempts have been made to homologize certain elements in the mammalian thalamus with the nucleus rotundus on the basis of relative size and shape. It is in reptiles that the mammillo-thalamic tract (bundle of Vicq d'Azyr) can first be recognized. It can only be defined, however, in certain forms, e.g., *Draco volans* (De Lange [36]). In most reptilian brains the tract is apparently undifferentiated from the diencephalic periventricular system of fibres, of which it was initially a part. The rostral fibres of this system, it would seem, become condensed to form a compact bundle which links up the mammillary region of the hypothalamus with the anterior part of the nucleus dorso-lateralis anterior as well as with a group of more medially situated cells belonging rather to the nuclei of the mid-line (*vide infra*, p. 438). This condensation of periventricular fibres is represented in the diagram (fig. 1 C). The anterior part of the dorso-lateral nucleus probably represents the antero-ventral nucleus of the mammalian thalamus. Why it should be the anterior part of the main somatic sensory element of the thalamus which thus becomes especially related to the hypothalamus is not clear, but it may perhaps be conjectured that as the dorsal, lateral, ventral and caudal regions are concerned with the reception of optic, tectal and lemniscal fibres, the rostral region is given over to this special development of the periventricular system.

At the tecto-thalamic junction near the dorsal surface a pretectal nucleus is to be recognized which is in close relation to the optic system and from which efferent tracts descend to the tegmentum of the mid-brain. This nucleus is apparently the equivalent of the pretectal nucleus of mammals which receives lemniscal fibres as well as sensory impulses relayed from the tectum.

In the mammalian thalamus (fig. 1 D) the main sensory nucleus is represented by the ventral nucleus or fillet nucleus. It forms the terminal station for the medial, the spinal, and the trigeminal fillets,

and it becomes differentiated from a mass of cells, which also gives rise to the geniculate bodies and the antero-ventral nucleus. All these elements comprise the lower functional levels of the thalamus which are mainly concerned with the reception of sensory impulses directly from the brain-stem and spinal cord, and from the hypothalamus. It is probable that the ventral nucleus represents an element which in the reptilia becomes differentiated to form the nucleus dorso-lateralis anterior and at least a part of the nucleus rotundus. The mammillo-thalamic tract has in mammals become a very well defined bundle which reaches its greatest development in higher mammalian types. In association with this fact the anterior nucleus in which it terminates attains its most complete definition in these forms (so far as its antero-ventral element is concerned). The less specialized part of the periventricular system persists as a more diffuse tract of fibres and intermingled cells linking up the hypothalamus with the mid-line nuclei of the thalamus. The pretectal nucleus is best developed in primitive mammals.

A distinctive feature of the mammalian thalamus is the development of an upper level (topographically and functionally speaking) which is not represented in submammalian forms. This occupies the dorsal part of the thalamus, above the ventral nucleus, from which it is more or less separated by transversely disposed intralaminar nuclei, and comprises such nuclear masses as the lateral nucleus and the dorso-medial nucleus (see fig. 4). These upper levels receive no significant afferent connections from lower sensory centres except by relays through the lower levels of the thalamus. They are related rather to the "association" areas of the cortex, whereas the nuclei of lower thalamic levels are connected with the sensory projection areas, and they exhibit a progressive increase in relative size and elaboration in higher mammalian types culminating in the primates where the association areas of the cortex attain to their fullest development.

GENERAL NUCLEAR CONFIGURATION OF THE MAMMALIAN THALAMUS.

In serial sections through the thalamus which have been stained to show the cells it is possible to recognize and define a considerable number of individual cell groupings which may be mapped out by limiting medullary laminæ and by the morphological type of their constituent cells. By reference to sections stained to show the fibres, these groupings may also be recognized and perhaps further subdivided on the basis of their fibre connections. In this way a variable number

of separate thalamic "nuclei" have been recorded by numerous observers. These nuclei are often poorly circumscribed and grade one into the other. It may be argued, indeed, that many of them hardly deserve to be defined as distinct nuclei, and that a difference in cyto-architecture, for instance, does not necessarily indicate any fundamental morphological or functional differentiation. Thus the appearance of the cells and their arrangement may be altered by the passage among them of fibre paths with which they are not directly connected, or by the mechanical pressure of adjacent structures. However, while freely admitting that some of the thalamic nuclei of descriptive anatomy are not necessarily to be regarded as functional units, it is certain that, as a preliminary to a more complete experimental and clinical investigation, an analysis based upon direct anatomical study is essential. Descriptive superfluities may be discarded later on if and when there are found to be such.

Broadly speaking, the thalamic nuclei may be divided into two groups: *principal nuclei* and *intra-laminar nuclei*. The former consist of fairly well defined and clearly differentiated groups of cells which are homogeneous in their morphology, are more or less circumscribed by surrounding medullary laminæ and are concerned predominantly with the reception of circumscribed fibre tracts. Such nuclei are represented for example by the ventral nucleus and its subdivisions which receive the fillet system of fibres, the anterior nucleus in which terminates the well-defined bundle of *Vicq d'Azyr*, and the geniculate bodies which receive the optic and the auditory tracts. These principal nuclei can usually be recognized without difficulty in the brains of different mammals. Among the principal nuclei and outlining them are fibre tracts which form medullary laminæ. These laminæ are strewn with cells of various types which are often closely packed and usually small and fusiform in shape; they form the intra-laminar nuclei. They are less well defined than the principal nuclei, they are irregular in outline and their fibre connections are usually diffuse. The latter, indeed, are difficult to determine because a large proportion of the fibres in the intralaminar nuclei are merely fibres of passage which are coursing in among the principal nuclei of the thalamus and inter-connecting the latter. There is no doubt that in some cases (e.g., the nucleus *paracentralis*) the cells of the intralaminar nuclei really comprise the peripheral zones of the adjacent principal nuclei, their appearance having been modified by the fibres which are interwoven with them. In the course of this paper detailed attention will be given to the principal nuclei of the thalamus only.

In fig. 2 a diagram is given representing schematic sections through the anterior, middle and posterior parts of the thalamus of a primitive and generalized mammal. From this diagram the main thalamic nuclei and their relative position may readily be apprehended. In the anterior section, the three elements of the anterior group of nuclei are shown, the antero-dorsal, antero-ventral and antero-medial nuclei. These three nuclei are the terminal station of the fibres of the bundle of Vicq d'Azyr or the mamillo-thalamic tract. The antero-dorsal nuclei are shown connected across the mid-line by a strand of cells

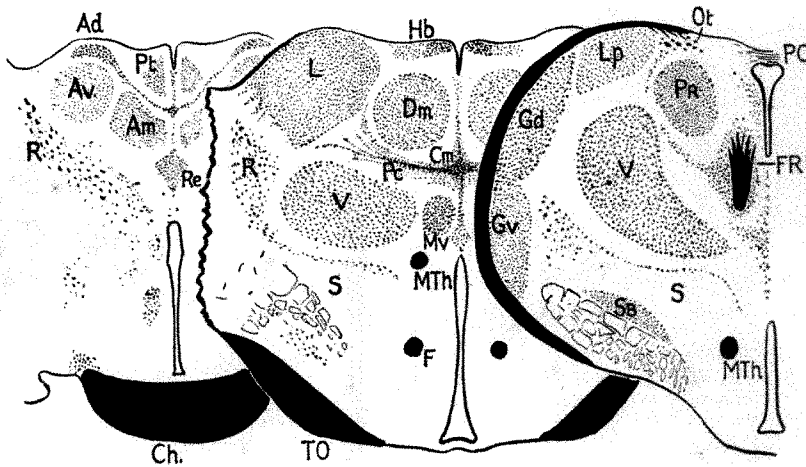


FIG. 2.—Diagram representing sections through the thalamus of a simple and generalized mammalian brain to show the relative position of the principal thalamic nuclei. *Ad.* Antero-dorsal nucleus. *Am.* Antero-medial nucleus. *Av.* Antero-ventral nucleus. *Ch.* Optic chiasma. *Co.* Nucleus centralis medius. *Dm.* Nucleus dorso-medialis. *F.* Fornix. *FR.* Fasciculus retroflexus. *Gd.* Dorsal nucleus of the lateral geniculate body. *Gv.* Ventral nucleus of the lateral geniculate body. *Hb.* Habenula. *L.* Lateral nucleus. *Lp.* Pars posterior of the lateral nucleus. *MTh.* Mammillo-thalamic tract. *Mv.* Nucleus medialis ventralis. *Ot.* Large-celled nucleus of the optic tract. *Pc.* Nucleus paracentralis. *PC.* Posterior commissure. *Pr.* Pretectal nucleus. *Pt.* Nucleus paratenialis. *R.* Nucleus reticularis. *Re.* Nucleus reuniens. *S.* Sub-thalamus. *Sb.* Nucleus subthalamicus. *TO.* Optic tract. *V.* Ventral nucleus.

which forms an interstitial nucleus of a commissure (commissura inter-antero-dorsalis). Above this commissure and close to the mid-line is the paratenialis nucleus. The mid-line nuclei are represented by the paraventricular nucleus and the nucleus reuniens. Ventro-laterally is the nucleus reticularis, consisting of cells scattered among the fibres of the thalamic radiations.

In the next section, through the middle part of the thalamus, the intralaminar nuclei associated with the periventricular system of fibres and with the commissural fibres of the massa intermedia form a cruci-

form arrangement which divides the cross-section of the thalamus into quadrants. Condensations of cells in the median line form a series of mid-line nuclei of which two are shown at this level, the nucleus centralis medius and the nucleus reuniens. The strands of intralaminar cells which extend laterally from the nucleus centralis medius among the commissural fibres form the nucleus paracentralis and the nucleus centralis lateralis, and are continuous rostrally with the commissure between the antero-dorsal nuclei. Below the paracentral and lateral central nuclei is the large ventral nucleus which is the end-station of the fillet system, and which is bounded ventrally by the ventral medullary

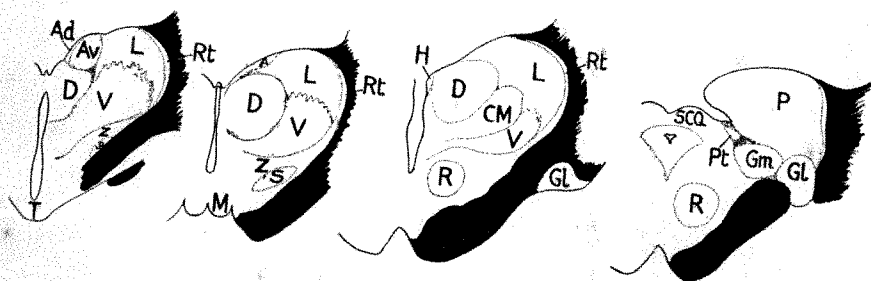


FIG. 3.—Diagram representing sections through the human thalamus to show the relative position of the main thalamic nuclei. *Ad.* Antero-dorsal nucleus. *Av.* Antero-ventral nucleus. *CM.* Centre median nucleus. *D.* Dorso-medial nucleus. *GL.* Lateral geniculate body. *Gm.* Medial geniculate body. *H.* Habenula. *M.* Mammillary body. *P.* Pulvinar (pars posterior of the lateral nucleus). *Pt.* Pretectal nucleus. *R.* Red nucleus. *Rt.* Nucleus reticularis. *S.* Subthalamus. *SCQ.* Superior corpus quadrigeminum. *T.* Tuber cinereum. *V.* Ventral nucleus.

lamina and, below this, by the zona incerta of the subthalamus. Close to the mid-line is the rounded nucleus medialis ventralis which further forwards merges with the antero-medial nucleus. The dorsal moiety of the thalamus which is marked off by the transverse intra-laminar nuclei contains the main part of the lateral nucleus and the dorso-medial nucleus. The former is small in primitive brains, but expands considerably in higher forms. The same observation may be made on the dorso-medial nucleus which is bounded laterally by the medial medullary lamina and medially by the paraventricular nucleus of the mid-line group of nuclei. Dorsal to it are seen the medial and lateral habenular nuclei which form a part of the epithalamus.

In the caudal section the fasciculus retroflexus of Meynert or habenulo-peduncular tract is shown descending to the interpeduncular ganglion, and embedded in an intralaminar nucleus, the nucleus para-fascicularis, which is differentiated from the caudal extremity of the paracentral nucleus. The ventral nucleus extends dorso-laterally to the

lateral medullary lamina. The optic tract is shown passing up the side of the thalamus and coming into relation successively with the ventral nucleus of the lateral geniculate body, the dorsal nucleus of the lateral geniculate body, the pars posterior of the lateral nucleus (which is continuous anteriorly with the main part of the lateral nucleus) and the large-celled nucleus of the optic tract. Just caudal to this level, the fibres of the optic tract reach the anterior colliculus of the mid-brain. Subjacent to the large-celled nucleus of the optic tract is the pretectal nucleus which lies at the tecto-thalamic junction, and is situated immediately behind the upper end of the fasciculus retroflexus. At a more caudal level the medial geniculate body replaces the lateral geniculate body. The relative position and size of the principal thalamic nuclei in the human brain are indicated in fig. 8.

For purposes of description, the principal thalamic nuclei may be grouped as follows:—

A.—*Lower levels of the thalamus.*

(1) Ventral group of nuclei, including the main ventral nucleus of the thalamus and its subdivisions, and the nucleus medialis ventralis.

(2) Anterior group of nuclei.

(3) Nuclei related to the optic tract, including the dorsal and ventral nuclei of the lateral geniculate body, the large-celled nucleus of the optic tract, and the pretectal nucleus.

(4) Medial geniculate body.

B.—*Upper levels of the thalamus.*

(1) Lateral group of nuclei, including the pars principalis, or main part of the lateral nucleus and its subdivisions, the pars posterior of the lateral nucleus, and the nucleus supra-geniculatus.

(2) The centre median nucleus.

(3) The dorso-medial nucleus.

The diagrams reproduced in this paper are purely schematic.

THE VENTRAL GROUP OF NUCLEI.

The ventral nucleus of the thalamus and the lemniscus system.—The dorsal part of the diencephalon may be regarded as a terminal sensory correlation centre where afferent somatic impulses are brought into functional relation with each other and through hypothalamic connections with impulses from olfactory and visceral centres. In primitive forms these sensory impulses are for the most part relayed from the tectum of the mid-brain and are carried almost entirely by the tecto-

thalamic connections, though even in the simplest brain (e.g., petromyzon and teleostean fishes) there exist more direct paths to the thalamus from lower levels which do not relay in the mid-brain. In simple mammalian brains these tracts become much more predominant and are represented by the spino-thalamic tracts from the dorsal horn cells of the spinal cord, the medial lemniscus from the terminal nuclei of the posterior columns of the spinal cord, the trigeminal lemniscus from the sensory nucleus of the fifth cranial nerve, the lateral lemniscus from the auditory nuclei in the medulla and the optic tract fibres. The fibres of these sensory tracts terminate in nuclear groups which are primitively parts of a homogeneous collection of cells forming part of the pars dorsalis diencephali. The termination of the optic and auditory tracts in the lateral and caudal regions of this common sensory centre leads to a local differentiation of the dorsal nucleus of the lateral geniculate body and the main part of the medial geniculate body respectively. From the greater part of the centre, which receives impulses of general sensation, the ventral nucleus of the thalamus and its subdivisions become progressively developed. In a mammalian brain of primitive type (e.g. the brain of a generalized insectivore) there is little intrinsic differentiation of the ventral nucleus; it is represented by a uniform collection of moderately large nerve-cells which form a group of a roughly spherical shape occupying approximately the centre of the diencephalon. This is the "noyau sensitif" of Cajal [5]. It is bounded in front by the reticular nucleus, the anterior nuclei, and the mammillo-thalamic tract, the latter curving up round its anterior convex surface. Behind it is limited by the fasciculus retroflexus and the nucleus parafascicularis. Dorsally, the ventral nucleus is separated by medullary laminae and intralaminar nuclei, such as the n. paracentralis and the n. centralis lateralis, from the dorsomedial nucleus, the lateral nucleus and the pulvinar, and below it rests on the subthalamus from which it is separated by the ventral medullary lamina. Medially it is related to the nuclei of the mid-line and laterally the lateral medullary lamina serves to mark it off from the lateral geniculate body and the pulvinar (see figs. 2, 3, 9 and 10).

In its simple undifferentiated form, the ventral nucleus is easy to define by its cytoarchitecture as well as by the medullary laminae which surround it. The terminal fibres of the fillet system sweep round the nucleus on all sides, though mainly from the ventro-lateral aspect, and, penetrating it, form a rich plexus of medullated fibres which tends to separate up constituent cells into clusters and to give to the whole

nucleus a characteristic lobulated appearance. In some cases the separation of the antero-ventral nucleus from the ventral nucleus is not very clear. In a form such as *Erinaceus* (the hedgehog), in which the optic tracts are small, the boundary between the dorsal nucleus of the lateral geniculate body and the ventral nucleus is poorly defined, and in the minute brain of the common shrew (*Sorex*) the ventral nucleus is continued caudally without interruption into the medial geniculate body. In higher mammals these structures are much more differentiated, but here there may be difficulty in defining the precise boundary between the dorsolateral portion of the ventral nucleus and the lateral nucleus. The rich fibre connections which develop between the ventral and lateral nuclei as they undergo progressive differentiation tend to break up the outlines of these two nuclear masses where they are contiguous with each other.

In larger mammals the tendency to "lobulation" of the ventral nucleus is expressed by the more complete splitting up of the nucleus into several elements which may be distinguished from each other with a varying degree of clearness by reference to intervening medullary laminae as well as by the character of their constituent cells. Thus Rioch [52], in carnivores, recognizes five subdivisions of the ventral nucleus, and in higher primates (lemur [47], cercopithecus [19], and man) a similar but still more complicated type of differentiation exists. The functional significance of these subdivisions is not yet known and, indeed, it is hardly profitable to attempt an investigation into this problem until their topography and homologies have been defined with more exactitude. The presumption is that each element is related to particular groups of fibres in the medial fillet, and if there is a definite spatial localization of fibres in the fillet according to their source of origin there is probably a localization of the same order in the ventral nucleus.

The shape of the ventral nucleus is influenced and modified by the development of adjacent nuclear masses. Thus in higher mammals the greater relative size of the dorsal nuclei of the thalamus, and especially the centre median nucleus, leads to a compression and flattening of its medial part and the nucleus expands considerably in a lateral direction. The ventral nucleus forms the main terminal station for the lemniscus system of fibres. These approach it mainly from the ventral aspect where they form a great part of the ventral medullary lamina, and, as Cajal has described, they enter the nucleus and break up into complicated terminal arborizations among its constituent cells. The main efferent

connections in mammals, on the other hand, are with the neopallium by way of abundant thalamo-cortical radiations. The ventral nucleus thus comes to form an important relay station through which somatic impulses are projected on to the cerebral cortex and it must therefore play a significant rôle in association with the evolutionary development and differentiation of the cortex. It is thus a matter of considerable interest to study the precise mode of termination of the lemniscus fibres and to note whether they end also in relation to thalamic nuclei other than the ventral nucleus. As we shall see, there is some uncertainty on these points and much of the evidence available is open to criticism, partly because of the confusion in terminology.

Wallenberg [60] investigated the destination of the fillet in rabbits. He found that fibres from the nucleus gracilis end in the ventromedial part of the ventral nucleus (as well as in the substantia nigra, zona incerta and hypothalamus), while those from the cuneate nucleus end in its middle and lateral parts. The trigeminal lemniscus from the spinal nucleus of the fifth nerve passes up in a dorsal position into the internal medullary lamina of the thalamus to reach the dorso-lateral angle of the ventral nucleus and the ventrolateral angle of the "medial nucleus." Unfortunately, it is not quite clear what Wallenberg understood by the "medial" nucleus, or whether he found evidence of degeneration of terminal fibres within the substance of this nucleus. In the rabbit only sensory tracts, the fibres of which spring from the most frontal part of the spinal cord and from the brain-stem, reach the thalamus; the secondary spinal paths mainly end in the hind- and mid-brain. From his figures [60] it seems that the "medial" nucleus to which he refers is the pretectal nucleus (prebigeminal or posterior nucleus of other authors), for it clearly lies caudal to the upper end of the fasciculus retroflexus, and it has been established by numerous observers that fillet fibres terminate here. His comparison of the relative size of this nucleus in the mouse and rabbit (which he compares to the relative size of the trigeminal fillet in these animals) also refers to the pretectal nucleus. My own studies certainly show no correspondence between the development of the trigeminal system and the dorso-medial nucleus (Monakow's nucleus medialis α) in different animals. It might be expected that a study of the brain of Ornithorhynchus would be of great interest in this respect. The normal thalamus of this monotreme has been studied in some detail by Marion Hines [28], but its structure seems to be so aberrant in many respects that it is not easy to be certain of homologies. Hines identifies a

"medial" nucleus which she states is connected with the striatum and the secondary medial olfactory centres; caudally it is continuous with a nucleus ventrolateralis, the rostral portion of which receives fibres of the trigeminal lemniscus while the posterior part is the termination of the medial lemniscus. It is improbable that any of these elements corresponds to the dorso-medial nucleus of the mammalian thalamus. On the other hand there is no doubt that the "n. ventrolateralis" of the monotreme thalamus is the equivalent of the mammalian ventral nucleus. In *Ornithorhynchus*, in which the trigeminal system is prodigiously developed, there is an astonishing hypertrophy of the ventral nuclear element, and it can hardly be doubted that these two features are interrelated. Moreover, if the dorso-medial nucleus is to be identified at all in this brain, it certainly is no larger relatively than in other mammalian brains of an average normal structure. Here, then, is additional evidence that the trigeminal fillet is terminally related to the ventral nucleus and not to the dorso-medial nucleus.

Perhaps the most extensive work on the ascending thalamic tracts is that of Probst [50], who collected serial sections of forty experiments in which the lemniscus was cut and was thus able to study the resulting degeneration in great detail. Probst found that the fibres from the gracile and cuneate nuclei end in the nucleus ventralis *a* (employing von Monakow's nomenclature). He followed a few across the posterior commissure into the caudal and medial part of the thalamus of the opposite side, but this latter observation is considered by other observers (e.g., Wallenberg) uncertain, since osmic granules are so frequently to be observed in the posterior commissure in normal material stained by the Marchi method. After lesions of the anterior funiculus of the spinal cord in the cervical region, Probst traced degenerated fibres through the lateral part of the medial fillet which ended in the ventral nucleus *a* of the same side as the lesion. These evidently represent the ventral spinothalamic tract. The fibres of the trigeminal lemniscus from the substantia gelatinosa were followed across the mid-line as fibræ arcuatæ into the most medial part of the medial fillet and thence into nucleus ventralis *a* and nucleus ventralis *b*, and also into the most caudal part of n. medialis *b* and n. medialis *c*. The two latter nuclei represent intralaminar nuclei, and Probst did not describe any fibres of the lemniscus system as terminating in the dorso-medial nucleus (von Monakow's nucleus medialis *a*).

Vogt [58] produced an experimental lesion in the nucleus cuneatus of a cercopithecine monkey and followed the degenerated fibres up in

the medial fillet. In the text it is stated that degeneration was noted throughout the medial fillet, though the accompanying figures indicate that it predominated in the lateral fibres. Most of the degenerated fibres terminated in a part of the ventral nucleus called the caudal ventral nucleus, or *v.a.*; and none were traced into the lateral nucleus or into the "noyau ventral intermédiaire." The author stresses the sharp line of demarcation between the ventral and lateral nuclei of the thalamus in regard to the distribution of degeneration granules. Some degenerated fibres also penetrated the "noyau semilunaire," or *v.b.* (another element of the ventral nuclear group), and a few were found in the capsule and in the substance of the centre median nucleus. This suggestion that some of the medial fillet fibres end in the centre median nucleus is also made by Dejerine, but it is a matter which requires further investigation (*vide infra*, p. 463). The plates which accompany Vogt's paper are not convincing on this point, and absence of terminal degenerated fibres in the centre median nucleus (or its equivalent in lower mammals) after a lesion involving the medial fillet, seems to be the general rule, as it was certainly in my own experiments [12]. There is evidence that the caudo-ventral part of the centre median nucleus is traversed by fibres of passage of the medial fillet to the medio-dorsal region of the ventral nucleus, and it seems probable that the degeneration found by Vogt represents these fibres. If any fillet fibres really terminate in the centre median nucleus, they must be extremely few and of minimal significance. Certainly there is no evidence, as far as I know, of trigeminal fibres terminating here, in spite of the statements to this effect in many modern textbooks. Vogt himself believes that trigeminal fibres reach the intermediate part of the ventral nucleus.

Cajal [5] has described the termination of the main fillet in the main part of the ventral nucleus, his *noyau sensitif*, but collaterals also end in relation to the pretectal nucleus. He further states that trigeminal lemniscus fibres send collaterals to the anterior and posterior semilunar nuclei and terminate in the zona incerta of the subthalamus. It is not quite clear what are the homologies of Cajal's semilunar nuclei; it seems probable, however, that they represent merely the anteroventral and posterodorsal marginal zones of the main ventral nucleus (and in the latter probably also the intralaminar group of paracentral and lateral central nuclei) where the rich permeation of ascending fibres leads to a local differentiation. If so, the trigeminal fibres end in the peripheral parts of the ventral nucleus. Cajal does not indicate that any of these fibres end in connection with the dorso-medial nucleus (his intermediate dorsal nucleus).

Huber and Crosby [31] believe that in the medial lemniscus, from the lateral to the medial border, are situated successively lateral spinothalamic, gustatory and proprioceptive fibres, and that, in their termination in the thalamus, these groups of fibres are distributed in the same order to different parts of the ventral nucleus in a latero-medial direction. This suggestion, however, still requires to be tested experimentally.

Papez [44], in a short note, describes the termination of the medial fillet after section of the tract in the tegmental region. The main site of termination is stated to be the "ventral and lateral nucleus." It is not possible to infer from this whether the lateral nucleus referred to is anything more than the lateral part of the ventral nucleus. A doubtful few of the fillet fibres were traced into the substantia nigra and the posterior commissure, but none were found to end in the zona incerta. Other fibres were followed to the posterior nucleus of the thalamus (= pretectal nucleus) along the course of the numerous thalamo-cortical fibres in this region.

Allen (1) describes in the guinea-pig the caudal part of the lateral region of the ventral nucleus (von Monakow's nucleus ventralis *a*) as the terminal for most of the medial lemniscus fibres, but he also describes some as ending in the caudal pole of the lateral nucleus. From a study of his figures, however, it seems that this lateral nucleus represents the dorsomedial part of the posterior ventral nucleus of Gurdjian's classical description. It may further be noted that Allen states that very few, if any, of the medial lemniscus fibres are distributed to the red nucleus, regio subthalamica or formatio reticularis. Rioch [54], from a study of normal material only, reports that in carnivores fibres from the medial division of the medial fillet enter the caudal pole of the lateral group of thalamic nuclei, but he was unable to follow these to their termination. There is, indeed, no certain evidence that any fibres of the fillet system end in those thalamic elements which—on the basis of recent descriptive anatomical work—come under the designation of lateral nucleus, and there is abundant negative evidence that they do not do so. In my own observations by Marchi's method, following lesions of the medial and trigeminal fillets in the rat [12], terminal degeneration in the thalamus was limited to the ventral nucleus (and the pretectal nucleus). Some of the degenerated fibres ran forward in the medial medullary lamina in the region of the paracentral and lateral central nuclei to the dorsal part of the ventral nucleus.

A critical survey of the observations of various authorities on the

mode of termination of the fillet in the thalamus shows complete unanimity in regarding the ventral nucleus as the main terminal nucleus of these sensory fibres. It is particularly to be noticed that many of these fibres sweep round the dorsal and ventral surfaces of the rounded ventral nucleus before penetrating it, and they thus course through intralaminar nuclei on their way. In Probst's account, nucleus ventralis *a* and nucleus ventralis *b* represent parts of the main ventral nucleus of the mammalian thalamus (corresponding probably to the pars arcuata and pars medialis of the ventral nucleus in the dog and cat according to Rioch). It is not easy to assess the evidence for the statement frequently made that part of the lemniscus system—and especially trigeminal fibres—end in the "medial nucleus." It seems that as a result of the looseness of nuclear terminology the results of experimental work have been persistently misrepresented by many authors. Thus Probst in his detailed investigation only claims to have found degenerated fibres after section of the fillet in n. medialis *b* and n. medialis *c*. These nuclei of von Monakow's terminology are the equivalent of n. paracentralis and n. centralis lateralis (Rioch). In other words they represent merely intralaminar nuclei in the medullary lamina which forms part of the capsule of the main ventral nucleus, separating the latter from the nuclei of the dorsal part of the thalamus, e.g., the lateral and dorso-medial nuclei. It seems probable that these degenerated fibres are components of the fillet which are sweeping round the ventral nucleus to reach its dorsal and rostral part. Unfortunately, the term "medial nucleus" has usually been applied in human descriptive anatomy to what is here called the dorso-medial nucleus, and the assumption has thus arisen that the latter is the site of termination of lemniscus fibres. So far as I am aware, however, no definite evidence has ever been adduced to indicate that—whatever may be the case with other nuclei sometimes included in the medial group—the dorso-medial nucleus receives such terminals. If fillet fibres actually terminate in connection with the cells of the intralaminar nuclei (n. medialis *b* and *c* of von Monakow) this need not qualify the statement that the ventral nucleus is the fillet nucleus (*noyau sensitif*), since these intralaminar nuclei largely consist of the peripherally situated cells of the ventral nucleus which are modified in appearance by their close relation with the interwoven fibres of the medullary lamina.

Relation of lemniscus system to the ventral part of the diencephalon.—In addition to the main termination of the medial fillet in the dorsal part of the diencephalon, there is evidence that some of

its fibres end in the subthalamus and hypothalamus. Thus Wallenburg traced fibres from the nucleus gracilis to the substantia nigra, zona incerta and mammillary body. The termination in the substantia nigra is accepted by several authorities (e.g., Elliot Smith [17], Winkler [63]), but the connections with the zona incerta and mammillary body are less certain. It is suggested that fillet fibres reach the latter by way of the peduncle of the mammillary body. It is probable that this peduncle consists, at any rate mainly, of ascending fibres (Wallenberg [59], Edinger [15], Cajal [5], Papez [44], Allen [1], &c.), and it is thought by some that these fibres are derived from the medial lemniscus and probably carry gustatory impulses. This problem remains yet to be settled, but it may be noted that Herrick has demonstrated the existence of anatomical connections between gustatory nuclei and the hypothalamus in the primitive brains of teleostean fishes, and it is not unlikely that this ancient pathway still exists in higher forms. Such a connection would fall into line with the clinical observation that disturbances of gustatory sensations are associated with lesions of the uncus of the temporal lobe, for the mamillary body is related directly to the uncus by way of the fornix system. Kappers [35] suggests that fillet fibres in the mammillary peduncle represent the spino- and bulbo-hypothalamic paths described in sub-mammalian forms.

Intrathalamic connections.—In a paper dealing with the lateral geniculate body [11] I noted the intimate fibre connection between the dorsal nucleus of this structure and the ventral nucleus, forming in primitive brains of mammals in which the visual apparatus is well developed (e.g., *Macroscelides*, *Pteropus* and *Tupaia*) a conspicuous and compact bundle. A similar connection between the ventral nucleus and the medial geniculate body has been studied with the degeneration method by Glorieux [22]. This author describes in the dog a fasciculus metathalamo-thalamo-corticalis which runs forwards from the medial aspect of the medial geniculate body and to a large extent terminates in the whole extent of the ventral nucleus. Rioch [54] has studied the intrathalamic connections of the ventral nucleus in normal carnivore and gives the following results: The pars anterior is mainly connected with the other elements of the ventral nucleus and has very few connections with the lateral, medial and anterior nuclear groups. The pars medialis is connected with the n. submedius (n. medio-ventralis), dorso-medial nucleus, n. lateralis and the periventricular system of fibres. The pars arcuata is connected with the n. submedius, n. lateralis, medial geni-

culate body, anterior and posterior colliculi, and the pars externa with the hypothalamus and subthalamus, including the zona incerta. In addition there is a free communication across the commissura mollis with the ventral nucleus of the opposite side. My own comparative studies indicate that the main intrathalamic connections of the ventral nucleus are: (1) With other nuclei of its own functional level, i.e., the medial and lateral geniculate bodies; (2) with the main part of the lateral nucleus, which in this respect bears the same relation to the main ventral nucleus that the pulvinar or pars posterior of the lateral nucleus does to the lateral geniculate body; and (3) with the periventricular system of fibres by which it is especially brought into functional relation with the hypothalamus and subthalamus. The connections with the dorso-medial nucleus seem to me to be relatively insignificant.

Connections with lower levels.—The fillet system has already been discussed. There are numerous tectal connections with the ventral nucleus, especially with its caudal third, probably conducting in both directions. These run largely in the lateral medullary lamina of the thalamus and are much more evident in the brains of primitive forms. In lowly vertebrates, indeed, most of the sensory impulses which are destined to reach the *analogue* of the mammalian ventral nucleus are relayed through the tectum by tecto-thalamic fibres.

A significant proportion of the fibres of the brachium conjunctivum, which emerge from the dentate nucleus of the cerebellum, terminate in the ventral nucleus, having passed up on the medial aspect of the red nucleus. This relation has been studied exhaustively in the guinea-pig by Allen, who found that in this rodent the cephalic end of the large lateral nucleus ventralis thalami (nucleus ventralis *a*) is the terminus for most of the thalamic fibres of the brachium conjunctivum. The only other element of the dorsal part of the diencephalon to which he could trace any of these fibres was a "medial nucleus" which, judging from his figures, probably is the equivalent of the nucleus parafascicularis. In the human brain, Probst describes fibres of the superior brachium ending in the more medial of the ventral nuclear group of the thalamus.

It may be relevant to note here that Sachs [55] records a descending degeneration in the posterior longitudinal bundle after a lesion involving the ventral nucleus, and he traced collaterals from these fibres to the nuclei of the fifth, sixth, eighth and tenth cranial nerves. These observations, however, have not been confirmed, and there is negative evidence against their acceptance.

Cortical connections of the ventral nucleus.—The rich connections between the ventral nucleus and the internal capsule by way of the thalamic radiations are very conspicuous in Weigert preparations of this region. There is reason to believe that the great proportion of these fibres extends to the cortex, but it is generally believed that at least some of them terminate in the caudate nucleus and putamen, forming a part of the thalamo-striate system. The precise relation of different parts of the ventral nucleus to various cortical areas is a question of considerable importance, but in spite of the work which has been done by numbers of investigators on this problem there still remains much uncertainty about it. This is mainly due to the great technical difficulties in approaching the problem experimentally. Many years ago von Monakow [43] studied the thalamo-cortical connections by the method of van Gudden, i.e., by removing portions of the cortex in young animals and searching for the atrophic changes which occurred in the thalamus after a considerable interval of time. It is generally conceded, however, that this method is unable to provide accurate results in a question of this kind. It has been recognized from the time of von Monakow and Cajal that the different parts of the thalamus are projected on to areas of the cortex which occupy relatively similar positions. Thus, fibres from the anterior part pass towards the frontal lobe, those from the posterior part towards the occipital lobe, and so on. Elliot Smith [16] has shown how this conception can be held to explain to a considerable extent the known distribution of cortical areas.

As the result of scattered observations on clinical cases, it is generally held that the ventral nucleus in man is mainly related by corticopetal fibres with the pre- and post-central gyri and with neighbouring parts of the frontal and parietal lobes, but more especially with the somæsthetic projection areas. The cortical radiations of the ventral nucleus in lower mammals, however, are probably more diffusely distributed over the neopallium in correlation with the less definite differentiation of the cortical fields and with their relative functional equipotentiality. There are scattered experimental observations dealing with this point and also an extensive report by Minkowski [42] on cortical connections in the monkey which gives a good deal of apposite information. Probst records that in the cat a lesion in the caudo-ventral nucleus leads to a degeneration which is distributed mainly to the coronary gyrus. Sachs [55], in the monkey, notes that thalamo-cortical fibres from the "ventral region of the lateral nucleus" (presumably equivalent to the ventral nucleus of most authors) are distributed only to the motor area

and the post-central gyrus. Minkowski states that in the monkey fibres run from the anterior part of *n. ventralis a* (*n. ventralis lateralis* of von Monakow) and the adjacent part of the *n. ventralis* anterior to the middle part of the ascending frontal gyrus (the arm area), and from the anterior part of *n. ventralis b* (*n. ventralis medialis*) to the opercular region of the ascending frontal convolution. Fibres pass from the middle part (in the anterior-posterior sense) of *n. ventralis a* to the middle segment of the area (arm area) and from the lateral part of the posterior segment of *n. ventralis b* to the post-Rolandic opercular region. For the parietal area (comprising cortical fields 5 and 7 of Brodmann) fibres pass from the posterior extremity of *n. ventralis a* and *n. ventralis b*. to the supramarginal gyrus, and from *n. ventralis c* to the posterior extremity of the supramarginal gyrus. Lastly, corticopetal fibres are described as connecting the anterior extremity of the *n. ventralis* anterior to (probably) the postero-inferior part of the frontal region.

In regard to cortico-thalamic connections of the ventral nucleus, the available evidence is more complete. Riese [51], in dogs, traced corticifugal fibres from the area precentralis to the ventral nucleus, especially *n. ventralis a*. In a cat, he found that lesions of the frontal lobes produced a fine degeneration in nucleus *ventralis c*. Biernond [2], in the rabbit, followed degenerated fibres into the caudal part of the ventral nucleus after cortical injuries, of which one involved fields 17 and 29, another the frontal lobes, and a third fields 29, 7, 17 and 18. In all these cases the degeneration in the ventral nucleus was slight. In monkeys, however, Biernond traced no corticothalamic fibres into ventral nucleus, and herein he is in complete agreement with Minkowski's experimental observations on the same animal. Poljak [48], in his observations on the degeneration following cortical lesions in the cat, does not specify the precise regions of the thalamus in which he found degenerating corticothalamic fibres. However, his figures indicate that in two of his cases, with injuries to the cortex of the parietal area (suprasylvian convolution), and of the insular areas, degenerated fibres penetrated into the ventral nucleus.

My own observations on the degeneration resulting from circumscribed lesions in different parts of the cortex in the rat's brain indicate that in this animal almost every part of the neopallium is connected by corticifugal fibres with the ventral nucleus except the anterior pole of the frontal lobe, the cingular areas, the striate area and probably the caudal margin of the temporal lobe. The latter two cortical areas are related to other thalamic nuclei of an equivalent functional level, i.e., the

lateral and medial geniculate bodies. Moreover, I found that these cortico-thalamic fibres terminate in regions of the ventral nucleus which correspond in their relative positions to the topography of the cortical area involved.

From a consideration of these results, it would appear that the corticothalamic connections of the ventral nucleus are much more abundant in the brains of primitive mammals, and that in the advanced types (e.g., primates) they are absent altogether. This is a point that requires careful consideration in connection with the theories of sensation which postulate a reciprocal fibre connection between the cortex and the ventral nucleus as the underlying anatomical basis of the cortical inhibition of thalamic activities.

The evolutionary differentiation of the ventral nucleus.—It has already been pointed out that the ventral nucleus of the mammalian thalamus is represented in lowly vertebrates (fishes and amphibia) by an undifferentiated and diffuse mass of cells in the pars dorsalis diencephali which Herrick has called the pars dorsalis thalami. This he showed (in amphibia) to be the great receptive centre of the diencephalon for somatic afferent impulses. The posterior part of this mass receives the spinal and lateral lemnisci, the middle and largest part receives tecto-thalamic fibres and possibly hypothalamic fibres representing the bundle of Vicq d'Azyr, while the dorsal part is the terminal for optic fibres. It is evident that the dorsal and caudal regions of this mass represent the *anlagen* of the geniculate bodies, while from the intermediate parts is differentiated the main ventral nucleus of the thalamus as well as other elements, such as a portion at least of the anterior nucleus.

In reptiles and birds the thalamus shows more nuclear differentiation. One of the most conspicuous nuclei in these vertebrates is the nucleus rotundus, a spherical mass of large cells which is usually well defined by a capsule of fibres and which occupies approximately the central region of the dorsal part of the diencephalon. In different species the nucleus rotundus merges to a greater or lesser extent with the nucleus dorso-lateralis anterior, a nucleus which is more diffuse but which contains the same type of cells. Both these nuclei are related by fibre connections with the lateral areas of the fore-brain and thus belong to what has been called the "somatic thalamus." As regards the nucleus rotundus we believe (with Ingvar [33], Crosby [31] and others) that the homologue of this characteristically sauropsidan nucleus is to be found in the ventral group of nuclei of the mammalian thalamus. It seems also probable that at least a part of the n. dorsolateralis anterior

(i.e., excluding that portion which is related to the mammillothalamic tract and therefore to be regarded as representing one of the elements of the anterior nucleus) is represented in the ventral nucleus.

The topographical position of the nuclear rotundus in relation to the mamillo-thalamic tract, the main part of the habenulo-peduncular tract, the subthalamus, and other elements, is suggestive of its homology with the ventral group of nuclei. The general similarity in appearance of these nuclei in sagittal sections is quite striking if the thalamus of a primitive mammal (e.g., *Erinaceus*, *Notoryctes*, *Sorex*) is compared with that of a reptile such as *Draco volans*, as figured by De Lange in his monograph.

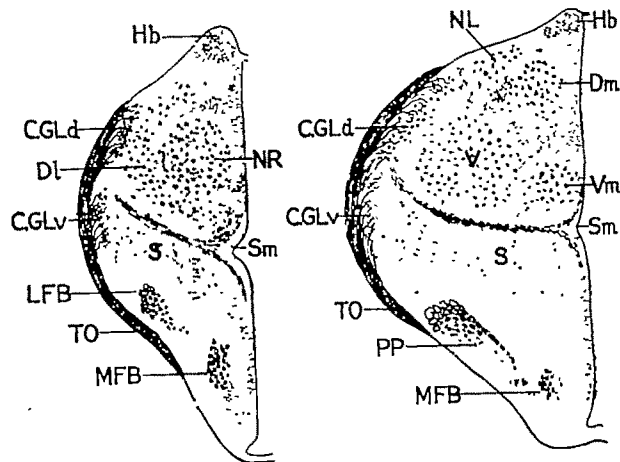


FIG. 4.—Schematic sections through the diencephalon of A, Reptile, and B, Mammal, illustrating the homologies of certain thalamic elements. CGLd. Dorsal nucleus of the lateral geniculate body. CGLv. Ventral nucleus of the lateral geniculate body. DL. Nucleus dorso-lateralis anterior. Dm. Nucleus dorso-medialis. Hb. Nucleus habenulae. LFB. Lateral forebrain bundle. MFB. Medial forebrain bundle. NL. Nucleus lateralis. NR. Nucleus rotundus. PP. Pes pedunculi. S. Subthalamus. Sm. Sulcus medius. TO. Optic tract. V. Nucleus ventralis. Vm. Nucleus medialis ventralis.

The relation of the commencement of the fibres of the habenulo-peduncular tract to the caudal extremity of the nucleus rotundus (passing laterally to it) has been used as an argument against this suggested homology, but it is not possible to rely on such a point, for the dorso-medial nucleus of mammals is not present in the reptilian thalamus and the origin of the habenulo-peduncular tract is thus brought into immediate relation with the homologue of the ventral nucleus, bearing much the same relation to the latter that it does to the

dorso-medial nucleus in mammals. The fibre connections of the nucleus rotundus favour its homologies with at least a part of the pars dorsalis thalami of amphibia on the one hand, and with at least a part of the mammalian ventral nuclear group on the other. Connecting it with the lateral somatic areas of the fore-brain in sauropsida (i.e., with the neostriatal regions) are abundant thalamo-striatal and strio-thalamic connections which are clearly the precursors of the internal capsule of mammalian brains. The question of cortical connections of the reptilian and avian thalamus has yet to be clearly decided, but if these are absent this does not necessarily invalidate the interpretation that the nucleus rotundus is strictly equivalent to a part of the ventral group of nuclei. It is to be presumed, indeed, that the development of a neopallial cortex must have been preceded by the differentiation of a ventral nucleus from which thalamo-cortical fibres were subsequently projected.

As regards ascending tracts De Lange [36] traced quinto-thalamic fibres in reptiles to the nucleus rotundus, and Huber and Crosby [30] regard it as probable (though they were unable to demonstrate it with certainty) that fibres of the spinal lemniscus and the trigeminal lemniscus terminate in the nucleus. The most conclusive evidence is that of Wallenberg [61] who by Marchi's method in birds followed ascending fibres from the nuclei of the posterior funiculi into the nucleus rotundus. This tractus bulbo-thalamicus is evidently the homologue of the medial fillet. He also found, associated with this bundle, fibres which terminated in the hypothalamus.¹

The relation of the nucleus rotundus to the lemniscus systems seems to settle beyond doubt its homologies with some part of the ventral group of nuclei of the mammalian thalamus. The suggestion that part of the nucleus dorso-lateralis anterior of the sauropsidan diencephalon is also to be regarded as the precursor of a part of the ventral nucleus is open to dispute on the ground that no direct lemniscus fibres have been traced to it. However, it is evidently very closely related to the nucleus rotundus both topographically and structurally; it is, like the latter, connected with the tectum by tecto-thalamic fibres and with the somatic areas of the fore-brain by the lateral fore-brain bundle, and its lateral portion in some reptilian forms undergoes differentiation as a terminal station for optic fibres in precisely the same way that the dorsal nucleus

¹ It is interesting that Wallenberg also recognized a quinto-frontal tract of fibres in birds which apparently conveys general sensory impulses right up to the neostriatum without interruption in the diencephalon. This tract appears to be an avian specialization.

of the lateral geniculate body appears in primitive mammals to be a delaminated portion of the lateral part of the ventral nucleus [11]. If it is remembered that in the evolution of the sensory paths of the central nervous system tecto-thalamic paths clearly precede the establishment of direct lemniscal connections, these points are all consistent with the interpretation advanced here.

The intrinsic differentiation of the ventral nucleus in the mammalian series has already been referred to above. Until we know more certainly the precise afferent and efferent connections of its various subdivisions it is useless to attempt further discussion on the significance of this differentiation. Presumably it is related to a regional localization comparable with that which is known to exist in the sensori-motor areas of the cortex with which it is so intimately connected. It is also possible that the differentiation may have a functional significance in relation to the different elements of sensation which pour into the thalamus, for it is known from the clinical observations of Head and Holmes [24] that on their approach to the thalamus sensory tracts become progressively segregated in accordance with the nature of the sensory impulses which they carry.

The differentiation of the ventral nucleus into component nuclear groups does not imply a lack of functional unity in the nucleus as a whole. The subdivisions are intimately linked up by intrinsic fibre connections and no doubt are mutually interdependent to a considerable degree. In this question, an observation of Minkowski [42] is particularly apposite. He noted that in cases of partial degeneration of the external thalamic nucleus of Burdach (which includes the ventral nucleus), following ablation of the ascending frontal or ascending parietal convolutions, some parts of the nucleus, although not degenerated, presented an atrophy (general diminution in volume, slight reduction in cell-volume, and reduction of intercellular substance). He believes that an alteration of this kind is to be explained by a certain degree of functional inactivity which is brought about in the whole of the external nucleus as the result of the degeneration of one of its component parts, and that the whole nucleus therefore represents an anatomical and functional unity.

Von Monakow and his workers have maintained that the ventral nucleus of the thalamus is connected only with the arm areas of the cortex, the lateral nucleus being associated with the leg areas. This seems, however, most unlikely to be the case (*vide infra*, p. 456).

NUCLEUS MEDIALIS VENTRALIS.

In the thalamus of lower mammals a distinct nuclear element lies close to the mid-line, ventral to the paracentral nucleus, medial to the ventral thalamic nucleus, and extending from the antero-medial nucleus anteriorly to the level of the fasciculus retroflexus behind. This is the nucleus medialis ventralis. It is actually in continuity rostrally with the antero-medial nucleus, so that in some forms at least (e.g., *Tarsius* [7]), it is not possible to distinguish between them on the basis of cyto-architecture. Whereas in lower mammals the nucleus is rounded and well circumscribed except anteriorly, in the higher primates it becomes more diffuse and is probably included under the heading of the nucleus submedius in some forms, while in others it is not recognizable as a separate unit. A survey of a comparative series indicates, indeed, that the nucleus medialis ventralis becomes progressively smaller and less distinct in the more advanced types. A study of normal Weigert preparations shows that the nucleus is connected by short fibres with the adjacent part of the ventral thalamic nucleus, with the medial medullary lamina, and with the periventricular system (Rioch [54]). In my own experiments on rats, I have not been able to trace any afferent fibres to the nucleus either as the result of cortical, thalamic or tectal lesions, nor have I found any evidence of Marchi degeneration in the nucleus after lesions involving the lemniscal system. In two cases in which lesions were localized in the nucleus medialis ventralis of one side, degenerated fibres were traced in abundance from the site of the lesion through the fasciculi of the internal capsule to the lenticular nucleus, but not extending further to the cortex. It would seem, therefore, that the nucleus is predominantly connected with the striatum. In this connection it may be noted that if there is any one thalamic element in the mammalian brain which can be homologized with the nucleus rotundus of the sauropsidan brain, it is the nucleus medialis ventralis. It satisfies topographical criteria in its relation to other diencephalic elements (bearing in mind that the dorso-medial and lateral nuclei of the mammalian thalamus are not represented as definite elements in lower vertebrates), and its striatal connections compare with the similar connections of the nucleus rotundus. Moreover, it is relatively better developed in primitive mammalian types, and in some (e.g., *Pteropus*, fig. 10, *Mv*) it is even enclosed by a well-defined capsule of medullary fibres in a manner which recalls the appearance in cross-section of the nucleus rotundus. This homology is suggested tentatively in the diagram shown in fig. 4.

THE ANTERIOR GROUP OF NUCLEI.

This group is represented typically by three elements in the antero-dorsal part of the thalamus, all of which are characterized by the fact that they are terminal nuclei of the mammillo-thalamic tract (bundle of Vicq d'Azyr). These are termed the antero-dorsal, the antero-ventral, and antero-medial nuclei. They vary in their relative development in different mammals. This variation has been dealt with in a previous communication where also reference was made to their phylogenetic history [9]. The antero-medial nucleus is to be regarded as a part of the "palæothalamus," differentiated from the mid-line nuclei, and apparently having no connection with the cortex cerebri. It is proportionately larger in primitive mammals and is probably the equivalent of the nucleus dorso-medialis anterior of reptiles. In higher mammals (e.g., primates) its identification is doubtful. It is almost certain that what has been called the nucleus antero-medialis in some higher mammals (nucleus anterior *b* of certain authors) is really a differentiated part of the antero-ventral element, and that the antero-medial element has become merged with the periventricular group of cells, probably forming a part of what has been termed by some the nucleus submedius.

The antero-dorsal nucleus in its well-developed form is distinguished by the large size of its cells. It cannot be certainly identified in some primitive and generalized mammals (e.g., *Erinaceus*), and in some forms it may reach an unusual size and definition (*Macroscelides* and rodents). In higher mammals it shows an increasing tendency to disappear, and in the higher primates is only a narrow band of cells capping the antero-ventral nucleus and sometimes grouped for description among the "nuclei disseminati." In most mammals the antero-dorsal nuclei of the two sides are interconnected by a well-marked commissure, the commissura inter-antero-dorsalis. The fibres of this commissure are well myelinated in lower mammals, but become unmyelinated in many of the higher types (e.g., *carnivora* [54]). The antero-dorsal nucleus has no representative in the reptilian thalamus.

The antero-ventral nucleus in higher mammals assumes a well-defined spherical form, clearly circumscribed by a medullary "capsule." It is termed the "anterior nucleus" in human descriptive anatomy and is responsible for the elevation of a rounded tubercle on the upper surface of the thalamus, the anterior tubercle. It is worthy of note that in many mammals an analogous tubercle is to be found in the same position, which is formed however by the rostral part of the lateral nucleus.

There has been some doubt regarding the relation of these elements of the anterior group of nuclei to the mamillo-thalamic tract. It is generally conceded that the fibres of this tract certainly end in the antero-ventral and antero-medial nuclei. Cajal described such a connection also for the antero-dorsal nucleus, but this has been more recently questioned. Such a connection is obvious, however, in *Macroscelides* in which the antero-dorsal element is relatively enormous, and Glorieux [22] has lately traced the termination of the mamillo-thalamic tract by Marchi degeneration into all the elements. This I have also established by my own experiments on rats [12]; in three cases in which the tract was sectioned on one side the degenerated fibres could be followed without



FIG. 5.—Section through the anterior group of nuclei of the thalamus of *Lemur Catta*. *Ad.* Nucleus antero-dorsalis. *Ant.* Nucleus antero-medialis. *Av.* Nucleus antero-ventralis. *F.* Fornix. *M.* Mamillo-thalamic tract (Bundle of Vicq d'Azyr).

difficulty into the antero-medial, antero-ventral and antero-dorsal nuclei on the same side. I found also that some of the fibres enter the inter-antero-dorsal commissure and, crossing over the mid-line, enter the antero-dorsal nucleus of the opposite side. This corresponds with the appearance seen in Weigert sections of normal material in *Macroscelides*. In these experiments descending degeneration was always found after a lesion involving the bundle of Vicq d'Azyr, which could be traced readily into the medial nucleus of the ipsilateral mammillary body. It seems probable, therefore, that Edinger's contention that this bundle also contains thalamo-mammillary fibres is correct, at least in the rat. As regards internuclear connections, the three elements of the anterior group of nuclei are intimately related to each other by short medullated fibres. According to Rioch, the antero-ventral nucleus receives fibres

from the dorso-medial nucleus, the lateral nucleus, the rostral end of the ventral nucleus and the nucleus centralis. The antero-medial nucleus is closely connected with the nuclei of the midline and thus is brought into relation with the periventricular system, of which, indeed, it is to be regarded as a differentiated part.

The extra-thalamic connections of the anterior nuclei still require further study. The antero-medial nucleus of primitive mammalian brains probably is not related directly to the thalamic radiations, it is essentially a part of the "palæothalamus." Thalamic radiations, on the other hand, can be traced into the antero-ventral and antero-dorsal elements in normal Weigert preparations.

The question arises as to whether these fibres are cortical in their origin or destination. As I indicated in my previous paper, there is evidence of an experimental and comparative anatomical nature to suggest that at least a part of the anterior nuclear group is in direct communication with the cerebral cortex, and most probably with the cingular areas. On the other hand, Sachs [55] has stated categorically that none of the fibres issuing from the antero-ventral nucleus in the cat (his nucleus dorsalis magnus) pass beyond the caudate nucleus. This was also described by Glorieux as the result of his experimental work on the dog's thalamus. I have recently observed in Marchi preparations of the rat's brain that lesions involving the area cingularis of the cortex (either in its anterior or its posterior part) are followed by the appearance of fine Marchi granules in the fasciculi of the thalamic radiations which permeate the antero-ventral nucleus, but no degeneration is found in the other elements of the group. Conversely, a lesion involving the antero-ventral nucleus leads to Marchi degeneration in the radial fibres which penetrate into the area cingularis of the cortex along the whole extent of the corpus callosum. Lesions of the frontal pole were not followed by changes in the anterior nuclei. From these data it seems justifiable to infer that the antero-ventral nucleus in the rat is related by projection fibres to the cingular cortex,¹ and it seems improbable that it has any direct relation to the frontal lobe, except in so far as the area cingularis extends into the medial surface of this lobe. The relation of the antero-dorsal nucleus to the cortex is not definitely proved; a study of normal Weigert preparations of insectivore

¹ Since this was written, Mr. R. H. Boggan and the author, working in collaboration, have succeeded in producing a localized electrolytic lesion in the antero-ventral nucleus of the cat with the use of the Clark-Horsley stereotaxic apparatus. Marchi preparations show degenerated fibres extending into the whole length of the cingular gyrus.

brains suggests that such a connection does exist. The peculiar features of the thalamus and cortex of *Macroscelides* furthermore suggest that this element may be in special relation with the very granular type of cortex found in the retrosplenial area. At the moment, however, this is a matter of speculation. The functional significance of the anterior nucleus is obscure. It has been pointed out above (*vide supra* p. 416) that the mammillo-thalamic tract is evidently a specialized portion of the periventricular fibre system. Since this fibre system appears to be concerned with the linking up of visceral neural mechanism in the hypothalamus with the somatic sensory centres of the thalamus, it may be conjectured that a similar function is subserved by the mammillo-thalamic tract. The anterior nucleus is certainly a receptive centre for impulses relayed from the hypothalamus through the mammillary body, and since the latter contains the main terminal nucleus of the fornix column it may be assumed that the functions of the anterior nucleus are closely bound up with those of the hippocampal formation. This, however, does not bring us much nearer the solution of the problem, for the functional significance of the hippocampus is itself a matter of speculation. We may note that even if the hippocampus was developed primarily as an olfactory cortical mechanism of some sort, it has evidently taken on other functions during its phylogenetic history, for it is a comparatively well-developed structure in the microsmatic human brain and even in the brain of anosmatic mammals. That the anterior nucleus must certainly be a thalamic element of some significance in the human brain is indicated by its size and differentiation, as well as by the size and definition of the mammillo-thalamic tract of which it is the terminal station.

THE RELATION OF THE OPTIC TRACT TO THE DIENCEPHALON.

It is well known that the fibres of the optic tract terminate mainly in the lateral geniculate body and the anterior colliculus of the mid-brain. There are, however, other terminal nuclei which, although relatively small, appear to be consistently present in those mammalian forms in which they have been sought. The course of the optic tract in the mammalian brain is schematically shown in fig. 6.

Before the optic tract reaches the lateral geniculate body in its course upwards and backwards, it gives off two small accessory tracts. The anterior accessory tract consists of fibres which leave the main tract as it passes obliquely across the crus cerebri. They have been identified in Marchi preparations and are described by some authorities (e.g.,

Loepp [38]) as piercing the peduncular fibres eventually to reach the subthalamic nucleus of Luys. I have identified this tract in the rat's brain after enucleation of one eye, but I was not able to follow the degenerated fibres further than the superficial aspect of the crus. Cajal [5] described in this position in rodents a thin stratum of cells which he stated to receive optic fibres. The posterior accessory optic tract leaves the main tract as the latter lies in topographical relation with the medial geniculate body. It forms a fine strand which runs obliquely in a caudo-ventro-medial direction across the crus, and is often known

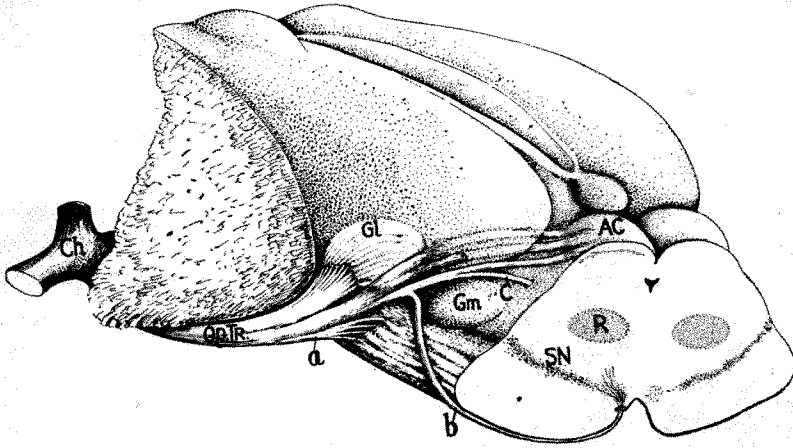


FIG. 6.—Terminal relations of the optic tract in the mammalian brain. AC. Anterior colliculus. a. Anterior accessory optic tract. b. Posterior accessory optic tract. c. Fibres passing to the large-celled nucleus of the optic tract. Ch. Optic chiasma. Gl. Lateral geniculate body. Gm. Medial geniculate body. Op. Tr. Optic tract. R. Red nucleus. SN. Substantia nigra.

as the tractus peduncularis transversus (see fig. 8). Its fibres end in the nucleus opticus tegmenti and the medial end of the substantia nigra, and some extend more dorsally into the tegmental region of the mid-brain [8]. For a discussion of these accessory tracts from the historical point of view, reference should be made to Tsai's paper on the optic tracts and centres in the opossum's brain [57].

Beyond the lateral geniculate body the optic tract passes into the stratum opticum of the anterior colliculus, many of its fibres penetrating the pulvinar to reach this destination, but the available evidence is against the commonly accepted statement that any retinal fibres end in the pulvinar. Weigert sections show that fibres of the mesencephalic root of the optic tract terminate in certain nuclear elements in the region of the tecto-thalamic junction; these are the large-celled nucleus of the optic tract and the pretectal nucleus. Experimental evidence

suggests that the fibres which enter the former nucleus are of retinal origin, while those which end in relation with the pretectal nucleus are probably derived from the lateral geniculate body (*vide infra*, p. 446).

LATERAL GENICULATE BODY.

The morphology of the lateral geniculate body has been dealt with in some detail in a separate publication [11]. The main conclusions may be briefly summarized here. In a generalized and primitive mammal the lateral geniculate body may be divided into a ventral and a dorsal nucleus. The ventral nucleus is the more primitive element and receives collaterals from the crossed fibres of the optic tract. It is a differentiated lateral segment of the subthalamus and is connected with the zona incerta. The dorsal nucleus is a differentiated lateral part of the ventral nucleus of the thalamus, and in some insectivore brains the two are not sharply separated from each other. The dorsal nucleus is connected by fibre tracts with the ventral nucleus of the thalamus, the pulvinar, the tectum and the area striata of the cerebral cortex. In the primates, the ventral nucleus shrinks in size until it consists of a small collection of scattered cells lying among the entering fibres of the optic tract, the corpus pregeniculatum. The dorsal nucleus, on the other hand, becomes relatively large and laminated. There is some evidence to suggest that in the primary intrinsic differentiation of the nucleus three cell laminæ become defined. This trilaminar type later gives rise to a six-layered nucleus in association with the appearance of a hemi-decussation of fibres in the optic chiasma. Minkowski [41] originally suggested that the alternate laminæ in the Anthropoidea are associated with the termination of crossed and uncrossed fibres of the optic tract. I have adduced evidence in support of this contention in two cases (monkey and human material) in which unilateral optic atrophy had occurred some time before death. If the six layers of cells in the lateral geniculate body of these types are designated 1a, 1b, 2a, 2b, 3a and 3b from the superficial aspect, it may be definitely stated, as the result of these observations, that crossed fibres of the optic tract end in laminæ 1a, 2b, and 3b, while uncrossed fibres end in laminæ 1b, 2a, and 3a.

THE LARGE-CELLED NUCLEUS OF THE OPTIC TRACT.

If the optic tract is followed up on its course to the anterior colliculus in a primitive mammal in which the visual system is well

developed (e.g., *Tupaia*, *Macroscelides*), it will be found, after passing over the pars posterior of the lateral nucleus, to come into relation with a superficially placed group of cells which are distinguished by their large size. This is the large-celled nucleus of the optic tract and it corresponds to Cajal's [5] "*noyau de la voie optique*." It lies along the anterior and lateral margins of the anterior colliculus, and Weigert sections show many fibres penetrating into it from the optic tract, as was originally described by Cajal. It is not conclusively proved that these fibres are of retinal origin, as the Marchi method has not been employed in those animals in which the nucleus is conspicuously developed. I have found a few degenerated fibres of the optic tract extending into the topographical equivalent of the nucleus in the rat after excision of the eye [8] and a similar observation is recorded in the rabbit by Loepp [38], who designates the collection of cells as the nucleus parageniculatus. It seems probable, therefore, that the optic tract fibres which terminate in the large-celled nucleus of the optic tract have their origin in the retina.

The nucleus primitively occupies a superficial position between the tectum and the pars posterior of the lateral nucleus, lying over the pretectal nucleus. In small primates it can readily be recognized, but with the progressive growth and caudal displacement of the pulvinar it shows a tendency to sink from the surface and to be flattened out to form a plate of cells along the junctional plane of the pulvinar and the mid-brain. Along the line of this "infolding" numerous small branches of the posterior cerebral artery penetrate into the brain. In higher primates the nucleus loses its distinctive features and is apparently incorporated in the nucleus limitans which is taken as the boundary line between the thalamus and the mid-brain. The efferent connections of the nucleus are obscure. In Weigert sections fibres may be seen emerging from its medio-ventral aspect and passing into the deeper layers of the anterior colliculus. Cajal described the axis cylinders of the cells as losing themselves in the white substance of the tegmentum of the mid-brain. There is some reason for the suggestion, based upon topographical position and relation to the optic tract, that the large-celled nucleus is homologous with the nucleus lenticularis mesencephali of the reptilian brain.

THE PRETETAL NUCLEUS.

In the brains of small mammals an oval and often well circumscribed nucleus of small and medium-sized cells is situated immediately behind the upper end of the habenulo-peduncular tract, extending in a caudo-

ventral direction to the medial aspect of the medial geniculate body. It lies in amongst numerous fasciculi of tectothalamic fibres. This is the pretectal nucleus, and, like many other thalamic nuclei, it has been mentioned and described under a variety of names. Cajal described it in rodents as the posterior, the bigeminal, or the prebigeminal nucleus, and defined it as lying in front of the superior corpus quadrigeminum and above the posterior semilunar nucleus (which is the intralaminar nucleus bounding the ventral nucleus postero-superiorly). Above, it is in contact with the optic fibres destined for the superior corpus quadrigeminum, and below it prolongs itself towards the medial fillet. It will thus be observed that the nucleus lies close to the dorsal surface of the brain at the tecto-thalamic junction, and it may well be disputed whether the structure is to be relegated in descriptive anatomy to the mesencephalon or the diencephalon. Recent evidence suggests that the nucleus contributes corticopetal fibres to the posterior thalamic radiations and thus justifies its inclusion among the thalamic nuclei [46]. On the other hand Winkler states definitely that the pretectal nucleus undergoes no degenerative changes after cortical ablation affecting most of the hemisphere [62]. In lower primates (e.g., *Microcebus* [10], *Lemur* [47]) it becomes more sharply separated from the nuclear masses which lie ventro-laterally to it by the appearance of a nucleus limitans, the developmental formation of which is dealt with elsewhere (*vide supra*, 444). In the description of the primate thalamus, this nucleus limitans has usually been taken as the boundary between mesencephalon and diencephalon, so the pretectal nucleus has usually not been regarded as a thalamic nucleus. It may perhaps most conveniently be regarded as a junctional nucleus linking up the tectum with the thalamus, and its intermediate character functionally is certainly indicated by its rich fibre connections with both these structures as well as by the fact that it is traversed by tecto-thalamic fibres. Tsai [57] has described it in the opossum as the pretectal nucleus. Gurdjian [23] deals with it in the rat as the posterior nucleus, and it is included by some other authors (Rioch [52], Papez [45]) in the nucleus of the posterior commissure. In my study of the thalamus in the tree-shrew [6], I called it the posterior nucleus, following Gurdjian's nomenclature. Further studies showed me that it corresponds clearly with Cajal's prebigeminal nucleus (which term is clearly synonymous with the more convenient name pretectal nucleus), and that, moreover, the term posterior nucleus had been used by different authors for other entirely different nuclear masses. In my description of the thalamus of

Tarsius [7] and Microcebus [10], therefore, I have used the name pretectal nucleus.

The variations in relative size of the pretectal nucleus in different mammals is noteworthy. In the rat it is particularly well defined; in *Macroscelides* it reaches a relatively enormous size, and in transverse sections has an even and clear-cut circular contour; in the hedgehog it is not so large, and its outline is less definite, but it is very well differentiated cyto-architecturally. The significance of such variations is not clear, for they do not seem to be consistently related to other differences in the general structure of the brain.

Fibre connections.—The pretectal nucleus has numerous connections with neighbouring nuclei and is also traversed by many fibres of passage; of these tecto-thalamic and cortico-tectal fibres are the most conspicuous.

Cajal long ago described collaterals from the main part of the medial fillet as ending in the nucleus, and this relation has been confirmed by several observers since. It seems that, in some cases at least, the pretectal nucleus has been mistaken for the "medial nucleus" of the thalamus, though the latter lies anterior to the habenulo-peduncular tract, while the pretectal nucleus lies behind it. This error partly explains the current legend that the "medial nucleus" is the terminal for lemniscus fibres and the subsequent inference that the "medial nucleus" is the homologue of the nucleus rotundus of the reptilian brain. It is not known what particular component fibres of the medial lemniscus reach the pretectal nucleus.

It has been mentioned above that the pretectal nucleus is in intimate relation with the mesencephalic root of the optic tract. In Weigert sections made in an appropriate plane, fibres from the optic tract can readily be seen to penetrate the nucleus from its dorsal and lateral aspect. It seems very doubtful, however, whether these fibres are actually of retinal origin, for, after section of the optic nerve in the rat (in which the pretectal nucleus is particularly well developed), I have been able to trace only a few degenerated fibres from the optic tract as far as the lateral margin of the pretectal nucleus, but not into its substance [8]. These few fibres seem rather to end in relation to a collection of cells which represents the large-celled nucleus of the optic tract in this animal. If the optic connections of the pretectal nucleus are not of retinal origin, they are probably derived from the lateral geniculate body from which, in Weigert sections, many myelinated fibres can be seen to emerge to join the optic tract on its way towards the pretectal nucleus. This geniculo-pretectal tract, indeed, is well

figured, but not described by Cajal in his classical textbook. That the optic connections are by no means the most important afferent connections of the pretectal nucleus is indicated by the fact that the variations in the relative development of this nucleus in different mammals show no direct relation to the relative development of the visual apparatus.

Loepp [38], experimenting on rabbits, found that some retinal fibres of the optic tract terminated in a collection of cells lying between the medial geniculate body and the superior corpus quadrigeminum, which had been called by Lewandowsky the nucleus parageniculatus. From his figures and descriptions it seems fairly certain that these cells do not represent the nucleus pretectalis, but the large-celled nucleus of the optic tract, and in this case Loepp's findings coincide with my own observations in the rat.

In carnivores, Rioch found that the pretectal nucleus is connected directly with the tectum, the caudal pole of the dorso-medial nucleus, the posterior part of the lateral nucleus and the nucleus parafascicularis, besides receiving fibres from the brachium of the superior corpus quadrigeminum and the medial lemniscus. There is no doubt, indeed, that the nucleus is very closely interconnected with the superior corpus quadrigeminum, and also with the immediately adjacent thalamic nuclei, by short fibres, and Weigert preparations also indicate that it contributes fibres to the posterior commissure. Hines [28] has described the pretectal nucleus in the thalamus of the *ornithorhynchus* and finds it has connections with the tectum, habenula, dorsal part of the tegmentum, "medial" nucleus and the lateral geniculate body.

As regards efferent tracts of the pretectal nucleus, sagittal sections of small mammalian brains show a descending pretecto-tegmental tract which can be traced down to the tegmental region of the mid-brain immediately dorsal to the substantia nigra, and this tract I have found to be especially conspicuous and well defined in *Erinaceus*. Tsai [57] has indeed traced a tract of fibres actually to the substantia nigra itself and he terms it the tractus pretecto-nigralis.

The cortical connections of the nucleus are a matter of some interest. There can be little doubt that it receives cortico-pretectal fibres, for I have found in the rat that, after a local lesion in the posterior part of the parietal region, degenerated fibres can be traced up over the posterior surface of the ventral nucleus in fasciculi of the posterior thalamic radiations as far as the pretectal nucleus [12]. Papez believes he has demonstrated experimentally corticopetal connections in rats

after a lesion involving the nucleus; the degenerated fibres follow the same course as the corticifugal fibres, but Papez [46] was unable to state definitely in what area of the cortex they terminated.

Evolution of the pretectal nucleus.—It has been stated that in silver preparations the pretectal nucleus is seen to be filled with a mass of neuropil indicating diffuse interconnections with surrounding cell masses. This appearance is distinctly primitive and suggests an ancient phylogenetic history. In amphibia, Herrick has described a region which he calls the pars intercalaris diencephali occupying a relative position in regard to the tectum, posterior commissure, fasciculus retroflexus, optic tract, &c., almost precisely identical with that of the nucleus pretectalis in mammals, and he states that efferent fibres pass from it caudoventrally to the tegmental region of the mid-brain (area tegmentalis lateralis). Although no direct optic tract connections have been described for the pars intercalaris, it is, like the pretectal nucleus, crossed superficially by the mesencephalic root of this tract as it courses from the pars optica thalami (= lateral geniculate body of mammals) to the tectum, and there can be little doubt that the two must be, in part at least, homologous. In reptiles, the pars intercalaris has evidently undergone considerable differentiation, and at least four cell collections can be recognized in the pretectal area, the n. pretectalis, n. geniculato-pretectalis, n. lentiformis and n. spiriformis. The nucleus spiriformis is regarded by some authors as merely a differentiated part of the n. pretectalis. Of these cell masses in reptiles, it seems probable that the n. pretectalis, n. geniculo-pretectalis and n. spiriformis together represent the true equivalent of the mammalian pretectal nucleus. The n. geniculo-pretectalis receives collaterals from the optic tract (in *Sphenodon* according to Cairney [4]), while both it and the n. pretectalis are connected with the lateral geniculate body (Edinger [15], De Lange [36], Huber and Crosby [30]). They are intimately related to the substantia grisea of the tectum and are traversed by tecto-thalamic bundles. Moreover, from both these collections of cells a fasciculus pretectalis descendens has been described (Cairney [4] &c.), which certainly represents the pretecto-tegmental tract present in mammals. Crosby thinks it possible that strio-tectal fibres of the lateral fore-brain bundle connect with the pretectal nucleus of the alligator's thalamus.

If this provisional interpretation of homologies is correct, it appears that the pretectal region in reptiles shows a higher degree of intrinsic differentiation than in mammals. But this is perhaps only to be anticipated when it is recognized that the evolutionary history of the

brain is largely a matter of the gradual shifting forwards of centres of functional control from lower to higher levels. The diencephalic sensory correlation centres in the reptile are as yet simple in structure and relatively unelaborated and the differentiation of the pretectal region may be looked upon as a structural indication that the tectum is beginning to hand over its activities as a correlation centre to the thalamus. The pretectal nuclei in birds, from the description of Huber and Crosby [32], seem to be still more differentiated, no doubt in correlation with the high development of the visual sense. Owing to the ventral displacement of the optic lobes and the consequent distortion of adjacent topography, it is difficult to establish satisfactory homologies of the pretectal elements in the avian brain.

The pretectal nucleus among mammalia shows a considerable amount of variability, and it is still uncertain what the significance of this is. As far as I am aware, it is found among all members of this group, including the primates. With the growth of other elements it comes to form a relatively smaller proportion of the bulk of the thalamus as a whole, but in proportion to the size of the tectum it does not seem to undergo much change.

From a consideration of its terminal relation to the fibres of the optic tract, Tsai has suggested that the pretectal nucleus of the opossum may represent the phylogenetic origin of the pulvinar of the primate thalamus. This, however, is certainly not the case, for by a study of a series of brains representing as close an approximation as possible to a phylogenetic series I have been able to identify without difficulty the pretectal nucleus in lower primates in which a pulvinar is also present. Further, there is of course no evidence that medial fillet fibres end in the pulvinar as they certainly do in the pretectal nucleus.

MEDIAL GENICULATE BODY.

In the brains of most primitive mammals the medial geniculate body forms a conspicuous tubercle at the caudal end of the lateral aspect of the thalamus. As is well-known, it receives a contribution from the lateral fillet, and it sends off the auditory radiations which are destined to terminate in the temporal region of the cerebral cortex. In most insectivore brains (e.g., *Erinaceus*, *Sorex*) the body is composed of cells of the same type as those which form the ventral nucleus of the thalamus, indeed the two are structurally continuous, so that it is impossible to define any boundary between them. This primitive condition seems to indicate that the medial geniculate body (as is the

case with the dorsal nucleus of the lateral geniculate body which represents an equivalent functional level) is a portion of the main sensory nucleus of the thalamus which has become secondarily differentiated in association with its auditory connections. In higher mammals, the medial geniculate body undergoes intrinsic differentiation. This is already to be observed in the progressive type of insectivore represented by *Tupaia*. In *Tarsius*, as in primates generally, it consists of a central mass of small cells in which the fibres of the lateral fillet appear mainly to terminate, caudo-ventrally there is a stratum of smaller cells which is related by fibre tracts to the zona incerta of the subthalamus, while dorso-laterally there is a larger-celled element which (as seen quite clearly in the brain of *Tarsius*) is derived from a caudal extension of the nucleus suprageniculatus, a part of the lateral group of nuclei (*vide infra*, p. 460). The caudo-ventral element, by analogy, is apparently the functional equivalent of the ventral nucleus of the lateral geniculate body, while the main central part of the medial geniculate body is the equivalent of the dorsal nucleus of the lateral geniculate body. The dorso-lateral element, it is suggested, bears the same relation to the main nucleus of the medial geniculate body that the pulvinar does to the lateral geniculate body. It contributes corticopetal fibres which join or form a part of the auditory radiations.

A study of the medial geniculate body in the mammalia indicates that its main part is a differentiated part of the ventral nucleus of the thalamus. This is not in accord with the generally accepted view that the nucleus isthmi of lower vertebrates is the precursor of the mammalian medial geniculate body. The nucleus isthmi of the reptilian brain certainly receives terminals of the lateral fillet system, and is connected with fibres of Gudden's supra-optic commissure (Kappers [35], Crosby [30]). It occupies, however, a very caudal position (lying caudal to the region of the posterior colliculus), and probably represents a mesencephalic element of the mammalian brain associated with the lateral fillet such as the nucleus of the lateral fillet, or perhaps the small-celled caudoventral element of the medial geniculate body.

In mammals, according to Rioch [54], only a proportion of the fibres of Gudden's commissure end in the medial geniculate body, the remainder continuing caudally, ventral to the medial geniculate body, to some lower centre. Larsell [37] has described a nucleus isthmi in amphibia (the frog), but already in the primitive *Necturus*, Herrick [25] has traced fibres of the lateral lemniscus system right up to the main sensory nucleus of the thalamus (his *pars dorsalis thalami*) from which

the lower functional levels of the thalamus generally have been derived. It is probable indeed that the reptilian homologue of the main part of the medial geniculate body is also to be sought for in the thalamus itself, either in the caudal part of the nucleus dorso-lateralis anterior or the nucleus rotundus.

In mammals the medial geniculate body is connected by short fibres with the ventral nucleus of the thalamus and with the nucleus supra-geniculatus (Rioch [54], Glorieux [22]). In addition it is reciprocally connected with the temporal cortex. Monakow [43] (in the cat and man), Zacher [66], Mingazzini [40], Löwenstein [39] (in man), and Yoshida [65] (in the rabbit) found cell-degeneration in the medial geniculate body after lesions involving the temporal lobe of the cortex. Ferrier and Turner (quoted by Yoshida) followed Marchi degeneration into the superior temporal convolution of monkeys after a unilateral lesion involving the medial geniculate body. The medial geniculate body requires more detailed structural analysis. It seems certain that in some descriptive accounts elements have been assigned to it which do not rightly belong to it. Thus in Yoshida's paper, his dorsal nucleus of the medial geniculate body (which was left almost unaffected by lesions of the temporal cortex) is undoubtedly the caudal extremity of the pars posterior of the lateral nucleus or pulvinar, which at this level comes into close topographical relations with the medial geniculate body proper.

THE LATERAL GROUP OF NUCLEI.

The main part of the lateral nucleus.—One of the distinctive features of the thalamus of higher mammals when contrasted with lower forms is the relative expansion of its lateral nucleus which also undergoes an intrinsic differentiation into secondary nuclear masses which are not always easy to define with certainty.

In a schematic diagram of the thalamus of a simple and generalized type of mammalian thalamus (fig. 2) it will be seen that the transverse intralaminar nuclei formed by the n. paracentralis and the n. centralis lateralis roughly divide the thalamus into upper and lower moieties. While the latter is occupied largely by the fillet nucleus, the dorsal half of the thalamus contains among other elements the lateral nucleus. The main part of the lateral nucleus forms the gray matter at the dorsal surface of the thalamus, bounded medially by the dorso-medial nucleus and the medial medullary lamina, laterally by the reticular nucleus and ventrally by the ventral nucleus, and extending rostrally to

the lateral aspect of the anterior nuclear group (n. antero-dorsalis and n. antero-ventralis), and caudally to the posterior end of the thalamus at the level of the posterior commissure. In the simply constructed brain of a primitive primate, the boundaries of the lateral nucleus are fairly distinct. In rostral planes it is made up of a uniform collection of medium-sized and regularly arranged cells, relatively free of a matrix of myelinated fibres. In Weigert sections, therefore, it stands out as a somewhat light area. At its anterior extremity it is closely related to the anterior nucleus and in some forms (e.g., dog, cat, lemur) it is partly

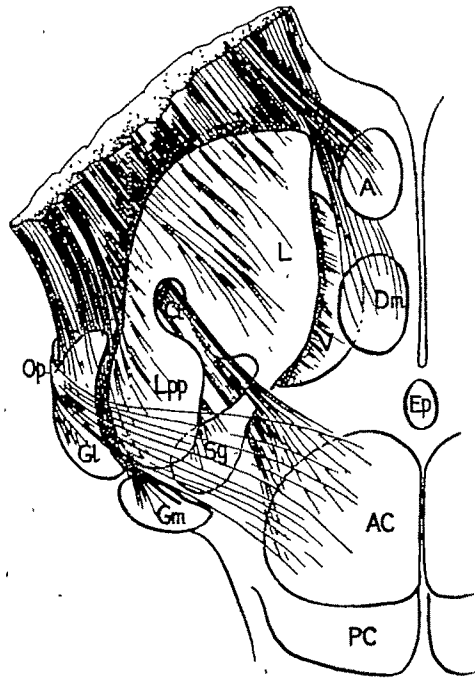


FIG. 7.—Schema of the thalamus to show the relations of the lateral nucleus and its extensions, viewed from the dorsal aspect. A. Anterior nucleus. AC. Anterior colliculus. Cl. Cortico-tectal tracts. Dm. Dorso-medial nucleus. Ep. Epiphysis. Gl. Lateral geniculate body. Gm. Medial geniculate body. L. Lateral nucleus, pars principalis. Lpp. Lateral nucleus, pars posterior. Op. Optic tract. PC. Posterior colliculus. Sg. Nucleus suprageniculatus. V. Ventral nucleus.

responsible for an oval elevation on the front of the dorsal surface of the thalamus, the anterior tubercle. This part of the lateral nucleus I described in my accounts of the thalamus in *Tupaia* [6] and *Tarsius* [7] as nucleus lateralis α .

Traced caudally, the lateral nucleus expands transversely and also extends to a deeper plane as the ventral nucleus recedes from the

dorsal surface. Here the deeper part of the nucleus loses the regularity of its cytoarchitecture and it is penetrated by abundant fascicles of medullated fibres. This region may be termed nucleus lateralis *b*, though it must be emphasized that there is no sharp line of division between the *a* and *b* elements, at least on the basis of normal histological appearance. Towards the posterior end of the thalamus, the lateral nucleus appears to send off two conspicuous expansions, of which one is intimately associated with the lateral geniculate body and forms the pars posterior of the lateral nucleus, while the other is similarly related to the medial geniculate body and forms the nucleus suprageniculatus. Such is the condition in a primitive primate such as *Tarsius*, in which these elements of the lateral nucleus are particularly distinct and, indeed, serve almost as a schematic basis for the interpretation of the nucleus in mammalia generally. The subdivision of the main part of the lateral nucleus into a dorsal part "*la*" and a ventral part "*lb*," which I have distinguished in *Tarsius*, seems to correspond broadly with a similar division made by Friedemann [19] in the cercopithecine monkey, Winkler and Potter in the cat [64], and Pines [47] in lemur, but our knowledge of the nucleus as a whole is so meagre that it is not possible to do more than suggest such homologies tentatively. In general features, the deeper nucleus lateralis *b* exhibits transitional characters between n. lateralis *a* and the ventral nucleus, and in more elaborate brains it may be practically impossible to indicate any precise boundary line between the lateral and ventral nuclei, at any rate on the examination of normal preparations. It may be suggested that the separation of the lateral from the ventral nucleus is altogether arbitrary and artificial, and that it would be better to include these parts of the thalamus in one descriptive group, such as Burdach's external nucleus of the thalamus. But although along their contiguous margins these two nuclei may merge with each other, the lateral nucleus as described here forms a mass of grey matter extending over the dorsal surface of the thalamus which can not only be broadly distinguished from the ventral or fillet nucleus by a difference in cyto- and myelo-architecture and its fibre connections, but also by the fact that it receives no fillet fibres. In simple non-primate brains the main part of the lateral nucleus is relatively a small thalamic element, considerably smaller, indeed, than its pars posterior. It does not extend so far rostrally relatively to the anterior nucleus, it does not reach so far back on the dorsal surface of the thalamus, and its transverse width is slight. This largely accounts for the fact that the thalamus in such

forms is more or less round in cross section, whereas in primate brains of an equivalent size the increase in width of the dorsal surface in conformity with the expansion of the lateral nucleus gives it more of a triangular section. Further, this expansion leads to a displacement of other nuclei, such as the external geniculate body, in a caudo-ventral direction.

Fibre connections of the lateral nucleus.—The fibre connections of the lateral nucleus are extraordinarily difficult to trace by the usual experimental methods, as it is traversed by so many fibres of passage, and it requires the greatest care to establish with certainty what fibres are actually interrupted here. From the study of normal Weigert sections of a variety of mammalian brains, there is no doubt that the main part of the lateral nucleus is in intimate fibre connection with the subjacent ventral nucleus and likewise with the other elements of the lateral nucleus, the pars posterior and the nucleus suprageniculatus. The connection with the ventral nucleus has been emphasized by Gurdjian [23] in the rat. This author also mentions connections with the superior thalamic radiations and, in its caudal part, with the tectum. In lower mammals the lateral nuclei of the two sides are linked together by commissural fibres which course through the intralaminar nucleus centralis lateralis. This commissural connection has been demonstrated experimentally in the dog by Glorieux [22]. Rostrally the lateral nucleus (n. lateralis *a*) is connected by internuclear fibres with the anterior nucleus, and especially with its antero-dorsal element. This is particularly obvious in an animal such as *Macroscelides* in which the antero-dorsal element attains a great development [9]. The relation between the two nuclei is also indicated by the fact that in some forms (e.g., *Microcebus*) the caudal part of the antero-dorsal nucleus is not clearly demarcated off from the anterior pole of the lateral nucleus as far as cytoarchitecture is concerned. Many fibres emerge from the medial aspect of the lateral nucleus to contribute to the medial medullary lamina and probably, through this, connect with the dorso-medial nucleus, n. parafascicularis (and the centre median nucleus); the pretectal nucleus and the tectum.

Rioch [54] made the following observations on the carnivore, thalamus. His pars anterior (= n. lateralis *a*) connects with the anterior nucleus (especially the antero-dorsal element), the dorso-medial nucleus, and the pars intermedia of the lateral nucleus. The pars intermedia and pars posterior (= n. lateralis *b*) have internuclear connections with the dorso-medial nucleus, the ventral nucleus, the pulvinar and n. supra-

geniculatus, the n. parafascicularis and tectum. In addition, some parts are said to contribute to the superior and intermediate thalamic radiations.

Evidently von Monakow's nucleus antero-dorsalis corresponds to n. lateralis *a*, while his nucleus lateralis represents our n. lateralis *b*. Rioch, in his detailed study of the thalamus of carnivore, recognizes a pars anterior (= n. lateralis *a*), a pars intermedia and pars posterior (together representing n. lateralis *b*).

The cortical connections of the main part of the lateral nucleus are still uncertain in their details. Von Monakow [43], basing his evidence

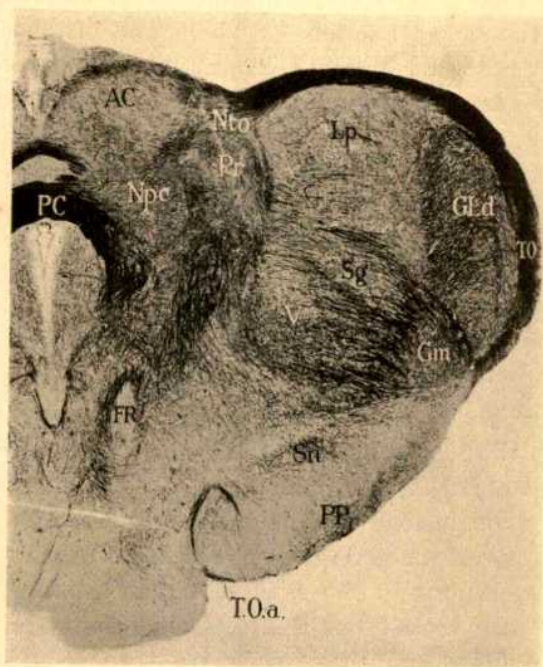


FIG. 8.—Transverse section through the caudal part of the thalamus of the fruit bat (*Pteropus*). AC. Anterior colliculus. FR. Fasciculus retroflexus. GLd. Dorsal nucleus of lateral geniculate body. Gm. Medial geniculate body. Lp. Pars posterior of the lateral nucleus. Npc. Nucleus of the posterior commissure. Nto. Large-celled nucleus of the optic tract. PC. Posterior commissure. Pr. Pretectal nucleus. PP. Pes pedunculi. Sg. Nucleus suprageniculatus. TO. Optic tract. TO.a. Posterior accessory optic tract. V. Posterior extremity of ventral nucleus.

on functional atrophy after cortical ablation, arrived at the conclusion that in mammals generally it is related to the parietal cortex, but that in man it is chiefly connected with the central convolutions. Minkowski [42] describes in the monkey corticopetal fibres from the anterior ex-

tremity of the dorso-lateral nucleus (=n. lateralis *a*) to the postero-superior part of the frontal region (superior frontal gyrus), from the middle third to the upper part of the precentral gyrus, from the posterior third to the upper part of the postcentral gyrus, and from the caudal extremity to the superior parietal lobule. He found no corticifugal fibres to the lateral nucleus.

Glorieux [22] concludes from his experiments on the dog that the cortical fibres of the lateral nucleus occupy the whole extent of the anterior limb of the internal capsule and are distributed to the anterior part of the parietal region anterior to the cruciate sulcus.

In regard to corticifugal fibres, Biernond [2] found evidence of these in the rabbit after cortical lesions of which one involved Brodmann's areas 17 and 29, a second areas 17, 29 and 22, and a third areas 7, 17, 18 and 29d. No degeneration was found in the lateral nucleus in this animal after an injury to the frontal region of the cortex. In the monkey, degeneration was present in the lateral nucleus after a lesion in the frontal region involving areas 6, 8, 4, 9, 10 and 11, but none was found after occipital lesions. In my own experiments on the rat's brain, a small lesion involving the most dorsal part of the parietal region of the cortex (just anterior to the area striata) led to Marchi degeneration in the main part of the lateral nucleus, and the result of thalamic lesions indicates that corticopetal fibres pass from the nucleus to the same region of the cortex. This cortical area, from its topographical position, is almost certainly the representative of the much more elaborate parietal association areas of higher mammals.

Minkowski's conclusions support the conception of von Monakow's school that the lateral thalamic nucleus is related to the "leg areas" of the central convolutions in the same way that the ventral nucleus is related to the "arm areas," but the facts that the lateral nucleus does not receive fillet fibres and that in higher mammals it expands out of all proportion to the size of the ventral nucleus, although in these forms there is no reason to suppose that the caudal half of the body requires a greatly increased representation in the thalamus or the Rolandic cortex, make it difficult to accept this interpretation.

On the whole, the evidence at hand suggests strongly that the lateral nucleus is mainly related to the parietal regions of the cortex, and this idea is supported by comparative anatomical evidence. A comparison of the brains of the tree-shrew (*Tupaia minor*) and the mouse lemur (*Microcebus murinus*) is especially instructive in this connection. They are readily comparable in size and general proportions, and a study of

their cortical lamination shows that the main sensory projection areas are of about the same extent in both. On the other hand, the "association areas" of the cortex, and especially the parietal and temporal regions, show a marked development in *Microcebus* as contrasted with *Tupaia*. In the thalamus, the ventral nucleus in both brains appears to be of much the same size, while the lateral nucleus in *Microcebus* is conspicuously developed in comparison with the same nucleus in the tree-shrew. It might be inferred from this that there is a functional relationship between the lateral nucleus and the "association areas" of the cortex, and, taking into account the fact that in *Tupaia* the medial geniculate body (related to the temporal area) is unusually small, it seems likely that the lateral nucleus is mainly related to the parietal cortex. This, indeed, is in harmony with the observation that throughout the mammalian series there is a close relation between the progressive elaboration of the lateral nucleus and the progressive expansion of the parietal region of the neopallium.

The Evolution and Functional Significance of the Lateral Nucleus.—The most striking feature of the main part of the lateral nucleus, from the comparative anatomical point of view, is its progressive enlargement and elaboration in the ascending mammalian scale. In primitive mammals, such as the common shrew (*Sorex*), it is extremely small, appearing at the dorsal surface of the thalamus immediately lateral to the anterior nucleus, but not apparent in caudal sections as a nuclear entity distinct from the ventral nucleus. In *Erinaceus*, the lateral nucleus is also small, and, judging from the figures in Tsai's paper [57], it is so in the Virginian opossum. In the tree-shrew [6], in which the brain has attained to a higher grade of development, the lateral nucleus is not only larger, but shows some degree of intrinsic differentiation. In the primitive primate, *Microcebus* (10), the lateral nucleus is larger, and in higher primates its increasing development is noteworthy. In these it is largely responsible for the great increase in the size of the thalamus and for the caudo-ventral displacement of some of the caudally situated nuclei such as the lateral geniculate body and the pars posterior of the lateral nucleus, and for the formation of a projecting posterior pole of the thalamus—the pulvinar. This increasing elaboration of the main part of the lateral nucleus certainly appears to run parallel with the progressive development of the so-called association areas of the cortex (especially if considered in comparison with the relatively more stationary ventral nucleus), and particularly with the parietal areas. This fact is suggestive of a direct functional relationship

between the main part of the lateral nucleus and the parietal cortex, and this, again, is supported to some extent by the study of fibre connections between these two parts of the brain.

The existence of a representative of the lateral thalamic nucleus in submammalian forms demands attention. If the main part of the lateral nucleus represents a higher functional level in the thalamus essentially associated with the more recently evolved regions of the neopallium, it will hardly be present as a distinct nucleus in the

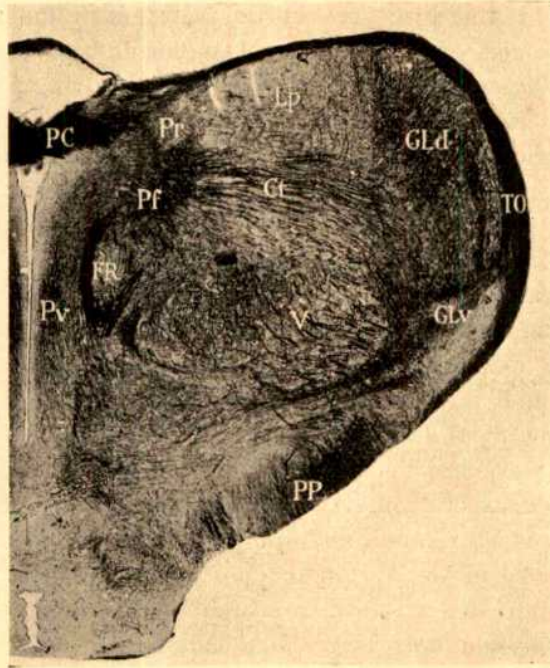


FIG. 9.—Transverse section through the thalamus of the fruit bat (*Pteropus*) at the level of the upper end of the fasciculus retroflexus. *Ct*. Cortico-tectal tracts. *FR*. Fasciculus retroflexus. *GLd*. Dorsal nucleus of lateral geniculate body. *GLv*. Ventral nucleus of the lateral geniculate body. *Lp*. Pars posterior of the lateral nucleus. *PC*. Posterior commissure. *Pf*. Nucleus parafascicularis. *Pr*. Pretectal nucleus. *Pv*. Periventricular system. *PP*. Pes pedunculi. *TO*. Optic tract. *V*. Ventral nucleus.

sauropsidan brain. In *Ornithorhynchus*, the main part of the lateral nucleus is evidently represented by a part of the nucleus dorso-lateralis as described by Hines [28], and it is small and but feebly differentiated. In reptiles it is, in our interpretation, absent altogether, or at the most is represented by a few scattered cells at the dorso-lateral extremity of the nucleus dorso-lateralis anterior.

This conclusion necessarily follows from the discussion on the homologies of the ventral nucleus in the reptilian thalamus.

The lateral nucleus of the thalamus thus appears to be a mammalian character, only attaining to a conspicuous size and differentiation in those brains in which the "association areas" of the cortex begin to occupy an appreciable proportion of the neopallium.

From its close association with the subjacent ventral nucleus of the thalamus, it may be inferred that the main part of the lateral nucleus represents a higher intrathalamic functional level related principally to the sensory impulses which reach the ventral nucleus by the fillet. These impulses, having reached the ventral nucleus where they are represented in a relatively elementary form, may be there brought into relation with and modified by afferent impulses which come in from other thalamic nuclei of an equivalent functional level (e.g., the geniculate bodies and the anterior nucleus), and passed on to the main part of the lateral nucleus by short internuclear connections where they acquire a re-representation.

The pars posterior of the lateral nucleus.—In the thalamus of a primitive and generalized type of mammalian brain the main part of the lateral nucleus sends off two caudal extensions, the pars posterior of the lateral nucleus and the nucleus suprageniculatus. The pars posterior consists of the same type of cells as the main part of the lateral nucleus, and it extends caudo-ventrally immediately above and behind the dorsal nucleus of the lateral geniculate body, its close relation with which is one of its most distinctive features. It is intimately connected to it by internuclear fibres, and the two structures show a close parallel development in different mammalian forms. Caudally the pars posterior comes into topographical relation with the medial geniculate body and the anterior colliculus, superficially it is covered by mesencephalic fibres of the optic tract, many of which penetrate it on their way to the tectum, and it is separated from the main part of the lateral nucleus and from the lateral margin of the ventral nucleus by cortico-tectal fibres which help to form what has been termed the lateral medullary lamina of the thalamus. In mammalian brains, in which a relatively large anterior colliculus is combined with a high differentiation of the area striata of the cortex, these cortico-tectal fibres form a well-defined tract, so that the pars posterior of the lateral nucleus is sharply demarcated from deeper structures. It also receives fibres from the main part of the lateral nucleus, and, at its caudal extremity, from the tectum. There is no evidence that it receives

impulses directly from lower levels. From the pars posterior of the lateral nucleus, cortical projection fibres pass forwards in close association with the optic radiations which leave the lateral geniculate body, and, turning laterally into the internal capsule, they occupy here a position immediately in front of the geniculo-cortical fibres. So far as they can be followed in Weigert preparations of normal material, they are distributed to the cortex directly anterior to the area striata. This point has not been conclusively demonstrated by experimental study, as it is difficult to produce a lesion which is strictly localized to the pars posterior of the lateral nucleus without involving adjacent elements, but in one experiment in which the nucleus was involved by a thalamic lesion in a rat's brain [12] I was able to trace Marchi degeneration into the lower and anterior part of the area striata and into a narrow zone of cortex immediately in front of and below this area.

I have elsewhere [7] dealt with the evidence that the pars posterior of the lateral nucleus is the homologue of at least a part of what, in higher primates, is termed the pulvinar. It is unnecessary to repeat all this discussion here, but it may be noted that the pulvinar and the pars posterior of the lateral nucleus are identical in their topographical relations (as regards adjacent nuclei and fibre tracts), in their intrathalamic connections, in their relation to the optic tract, and almost certainly in their cortical connections. The conclusion is reached that the thalamic element included in the term "pulvinar" is by no means a distinctive feature of the primate diencephalon. It is present and may even attain to a relatively large size in the brains of primitive mammals. A definite projecting pole at the caudal extremity of the thalamus to form a "pulvinar" is foreshadowed in *Tarsius*, and is dependent on the progressive increase in size of the main part of the lateral nucleus which leads to a displacement caudally of the pars posterior. Brouwer [3] has emphasized the fact that no retinal fibres terminate in the pulvinar, which is therefore not one of the primary optic centres of the brain. I can confirm this observation in the rat [8] as in this mammal, after section of the optic nerve, Marchi degeneration in the pars posterior is confined entirely to the fasciculi of the mesencephalic fibres of the optic tract which pass through it to reach the stratum opticum of the anterior colliculus, and there is no evidence that any of these fibres terminate in the nucleus.

Nucleus suprageniculatus.—In the primitive primate, *Tarsius*, the caudal extensions of the lateral nucleus of the thalamus are particularly

easy to define. The pars posterior or pulvinar is clearly circumscribed by the relatively large cortico-tectal tracts; the other element, the nucleus suprageniculatus, is also sharply demarcated and can be readily traced by the differentiation of its cytoarchitecture as well as by the medullary laminæ which enclose it. It reaches in a caudo-ventro-lateral direction to the medial geniculate body, and ultimately can be traced as a continuous tract of cells into the dorso-lateral part of the medial

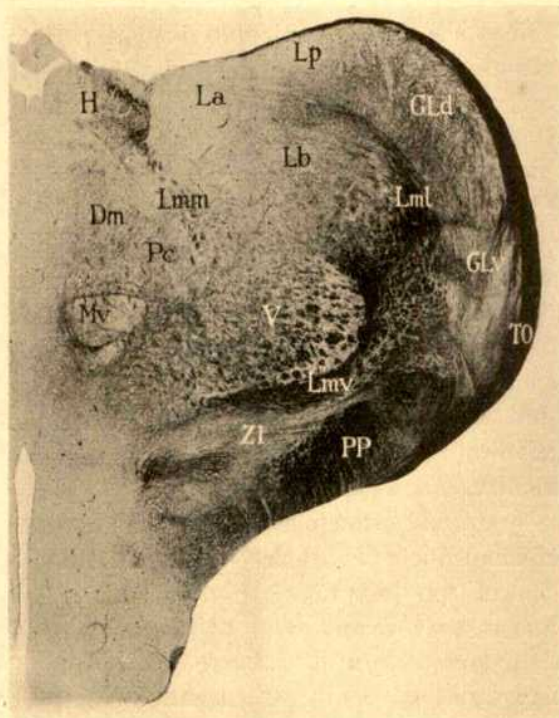


FIG. 10.—Transverse section through the middle of the thalamus of the fruit bat (*Pteropus*). *Dm*. Nucleus dorso-medialis. *GLd*. Dorsal nucleus of the lateral geniculate body. *GLv*. Ventral nucleus of the lateral geniculate body. *H*. Nucleus habenulæ. *La*. Pars principalis of the lateral nucleus, subdivision, *La*. *Lb*. Pars principalis of the lateral nucleus, subdivision. *Lb*. *Lml*. Lateral medullary lamina. *Lmm*. Medial medullary lamina. *Lmv*. Ventral medullary lamina. *Lp*. Pars posterior of the lateral nucleus. *Mv*. Nucleus medialis ventralis. *Pc*. Nucleus paracentralis. *PP*. Pes pedunculi. *TO*. Optic tract. *V*. Ventral nucleus. *ZI*. Zona incerta.

geniculate body with which it becomes incorporated. The nucleus suprageniculatus has been described and figured in the carnivore brain by Rioch [52], where it occupies a topographical position similar to that of *Tarsius*. It has also been described by Friedemann [19] in *Cercopithecus*. In the higher primates it is much less well defined and

its connections are difficult to make out. Rioch [54] mentions connections of the nucleus with the medial geniculate body, with the nucleus lateralis, with the tectum and with the medial medullary lamina. Fibres from it also run into the internal capsule in close association with the auditory radiations which spring from the main central part of the medial geniculate body. From a consideration of its relation to the main part of the lateral nucleus and its fibre connections it seems reasonable to suggest that the nucleus suprageniculatus has the same functional relation to the medial geniculate body that the pars posterior of the lateral nucleus has to the lateral geniculate body. This, however, is a question which demands further inquiry.

CENTRE MEDIAN NUCLEUS.

One of the most conspicuous and sharply defined elements of the human thalamus is the centre median nucleus of Luys. It occupies the caudal part of the thalamus, and reaches out in a dorso-lateral direction from near the mid-line between the dorso-medial nucleus above and the ventral nucleus below. Attempts to establish the homologies of the nucleus have resulted in discordant opinions, mainly because attention has not been given to phylogenetic considerations in the comparison of one brain with another. Its fibre connections also offer considerable difficulty, as it is penetrated by fibres of passage which run between the mid-brain and other parts of the thalamus.

The centre median nucleus is clearly distinguishable in the monkey [19] and the larger lemurs [47]. In the latter it is not so well circumscribed, and it merges caudally with the nucleus parafascicularis which encloses the upper part of the habenulo-peduncular tract. In Tarsius [7] it may also be recognized without difficulty; it occupies a relatively more dorsal position than in the higher primates, for in the latter the larger dorso-medial nucleus displaces it ventrally. In the small lemurs (e.g., *Microcebus murinus* and *Microcebus coquerelli*) the nucleus is less well defined and appears to be a rostro-lateral extension of the parafascicular nucleus. Still lower in the mammalian scale, in the tree-shrew (*Tupaia minor*) [6] the nucleus is much less evident, but even here it can be detected as a small triangular mass of cells which appears as a feebly-marked differentiation of the caudal part of the paracentral nucleus, but which is not clearly demarcated from either the paracentral nucleus or the nucleus parafascicularis. A comparison of a graded series which approximates as closely as possible to a true phylogenetic series indicates, indeed, that the centre median nucleus

arises as a specialization of the caudal end of the paracentral nucleus, which is itself an interstitial nucleus lying in the medial medullary lamina. Thus in its primitive form the centre median nucleus is an intralaminar nucleus penetrated by fibres of the medial medullary lamina. As it develops it attains to the status of a principal nucleus which becomes encapsuled by medullary fibres. Weigert sections show that it is in intimate fibre relation with the medial medullary lamina, and through this is brought into relation mainly with the tectum behind and in front with the nuclear elements which make up the dorsal moiety of the thalamus. I have suggested that it may be regarded therefore as an integrating mechanism related to that part of the thalamus in which progressive differentiation and growth are most obtrusive in the higher primates, and that its great development in the human brain is explicable from this point of view. This interpretation is not in accord with other views which have been advanced on its significance. Recently, however, Rioch [53] has advanced evidence to support the thesis that the centre median nucleus belongs neither to the lateral nor the medial group of thalamic nuclei, but represents a local elaboration of the interstitial nucleus of the medial medullary lamina. It has been stated that it receives fillet fibres; this partly rests upon the experimental evidence of Wallenberg, who traced Marchi degeneration into the medial medullary lamina in the rabbit after lesions involving the trigeminal fillet, and suggested that this termination of the degenerated fibres in the rabbit is homologous with the centre median nucleus of higher primates. This is, however, open to question, and my own experiments on the rat indicate that, although some degenerated fibres can be traced into the medial medullary lamina after a lesion involving the fillet system, they appear to be fibres of passage on their way to the dorsal aspect of the ventral nucleus. Vogt described a slight Marchi degeneration extending into the centre median nucleus of the monkey after destruction of the posterior column nuclei; this requires corroboration and it is also necessary to exclude fibres of passage which penetrate the caudo-ventral part of the centre median nucleus. An examination of a foetal human brain at the twenty-fourth week (for a study of which I am indebted to Professor Lucas Keane and Dr. Hewer), in which the medial fillet first begins to become myelinated, shows that fillet fibres course through the caudo-ventral part of the centre median nucleus, but at this stage the greater part of this nucleus is free of myelinated fibres. Whatever the significance of the centre median nucleus, its progressive development in the mammalian series, as shown by comparative

anatomical studies, indicates conclusively that it is far from being a primitive formation.

THE DORSO-MEDIAL NUCLEUS.

Situated in the dorsal moiety of the thalamus above the level of the paracentral nucleus and close to the mid-line is a group of medium-sized cells which can be distinguished with little difficulty in most mammalian brains. This is the dorso-medial nucleus. It is bounded laterally by the medial medullary lamina, medially by the paraventricular nucleus, rostrally it extends forwards to the anterior nucleus, and caudally it is limited by the fasciculus retroflexus. Reference has already been made to this nucleus in discussing the ventral nucleus of the thalamus and its connections and homologies, and it was pointed out that, largely as the result of a confusion of nomenclature, the dorso-medial nucleus is often described as the terminal station of fibres of the trigeminal fillet, as the equivalent of the reptilian nucleus rotundus, and as a representative, therefore, of the phyllogenetically more ancient part of the thalamus. The common description of the nucleus as a component of the "medial group" of thalamic nuclei which are often regarded as "palæothalamic centres" has, I think, added to a misconception of its true significance. The nucleus is the equivalent of v. Monakow's nucleus medialis α , of the nucleus medialis of human descriptive anatomy, and of the nucleus medialis dorsalis of many recent authors. The significance of the nucleus is indicated rather by its dorsal position—for it is developed essentially in relation to the upper levels of the thalamus—and it seems advisable to emphasize this fact by terming it the nucleus dorso-medialis.

A survey of a series of mammalian brains shows that in the more advanced types the dorso-medial nucleus becomes progressively larger, better defined and increasingly differentiated. In man, indeed, it seems to have attained the height of its development in these respects. In primitive mammals it consists of a few and scattered cells, and its limits are by no means clear cut. In higher types the constituent cells increase in number and become more compactly arranged. In the primates, an intrinsic differentiation is to be found, so that a medial large-celled and a lateral small-celled element can be distinguished. The differentiation can be made out on the basis of myeloarchitecture as well as on the basis of cytoarchitecture. This progressive elaboration of the dorso-medial nucleus in the mammalian scale is hardly consistent with the idea that the nucleus is a primitive thalamic element. It may be repeated here that no evidence has ever been adduced to suggest that it receives fillet fibres. Wallenberg's implication that in different mammals there

is a direct relation between the size of the dorso-medial nucleus and the development of the trigeminal system is due to an error of interpretation—his diagrams show that he is really referring to the pretectal nucleus (which lies *behind* the fasciculus retroflexus). Moreover, in *Ornithorhynchus* [28], in which the trigeminal nerve and its nuclei attain to prodigious proportions, there is no defined element in the thalamus which can be identified as the dorso-medial nucleus. In the interpretation adopted here (*vide supra* p. 434), the dorso-medial nucleus is not represented in the reptilian thalamus—it is essentially a mammalian structure.

The dorso-medial nucleus is intimately related to the fibres which course through the medial medullary lamina. Through these fibres it is probably brought into relation with all the neighbouring elements which form the dorsal levels of the thalamus, especially the lateral nucleus and the centre median nucleus. Its caudal extremity receives fibres which emanate from the nucleus parafascicularis and the deeper strata of the tectum. Horsley and Clarke [29] found fibres of the superior cerebellar peduncle ending in the "nucleus medius" in experimental animals. Rioch describes internuclear connections with the medial part of the ventral nucleus and with the periventricular system of fibres as well as with the nuclei of the mid-line (especially nucleus rhomboidalis). These periventricular connections, according to this author (whose observations are based on the examination of normal Weigert material), connect the dorso-medial nucleus with the nucleus hypothalamicus posterior, the nucleus supramammillaris and the tegmentum. I have been able to follow degenerated fibres into the periventricular system as the result of a small localized lesion involving the dorso-medial nucleus in the rat, though I was not able to trace them as far as the hypothalamus. Nevertheless, the intimate connection between the dorso-medial nucleus and the periventricular system and the nuclei of the mid-line is an important fact, and there can be little doubt that through this system the nucleus can be brought into direct functional relation with the activities of the hypothalamus. Sachs [55] found degenerated fibres in the centre median nucleus after a lesion involving the "medial nucleus" (which is probably the equivalent of the dorso-medial nucleus), and he traced efferent fibres also from the medial nucleus to the caudate nucleus and probably to the lateral nucleus of the thalamus. He maintained, however, that it had no cortical connections. It is, however, well established that the dorso-medial nucleus receives components from the thalamic radiations,

most of which run up in a dorsal and medial direction from the inner part of the internal capsule through the ventral nucleus to reach the ventro-lateral aspect of the dorso-medial nucleus. The question arises as to whether these fibres are of cortical origin. V. Monakow [43] postulated a fibre connection between the "medial" nucleus and the frontal convolutions in man. Dejerine [14] reported a case in which a lesion of the frontal lobe was followed by degeneration of the anterior part of the "medial" nucleus. Minkowski [42] describes in the monkey corticopetal fibres from nucleus medialis *a* (dorso-medial nucleus) to an extensive area of the frontal region, reaching forward to the frontal pole. He does not mention any corticofugal fibres related to this nucleus in his experimental studies of corticothalamic connections. Riese [51] found in the dog that a lesion of the precentral region led to a fine Marchi degeneration in the region of nucleus medialis *a*, and nucleus medialis *b*, and he quotes C. and O. Vogt as accepting a corticothalamic connection from the precentral cortex to nucleus medialis *a*. Biernond [2] describes degenerated fibres ending in the nucleus medialis thalami after a lesion in the frontal lobes of the rabbit (involving Brodmann's areas 4, 3 and 1). In my own experiments on the rat's brain I found that lesions of the frontal pole of the cerebrum gave rise to degenerated fibres which could be traced in continuity into the dorso-medial nucleus, and, conversely, lesions of the dorso-medial nucleus are followed by Marchi degeneration in fibres which can be traced in the reverse direction to the frontal pole. These fibres occupy the most medial fasciculi of the internal capsule, and course forwards in close topographical relation to the septal region near the medial surface of the hemisphere. There is abundant reason to believe, therefore, that there exists a direct fibre relation between the dorso-medial nucleus and the frontal cortical areas, and it is a matter of some significance that in the mammalian series there appears to be a close parallel between the progressive development of the prefrontal areas of the cortex and progressive elaboration of the dorso-medial nucleus. Such a relation further strengthens the opinion that the dorso-medial nucleus is not represented by any nuclear homologue in the sub-mammalian thalamus.

The functional importance of the dorso-medial nucleus would seem to depend very largely upon its connections with the frontal lobe of the cerebral hemisphere on the one hand and with the periventricular system on the other hand. The periventricular system, as already indicated, consists of median collections of nerve-cells (nucleus reuniens,

nucleus rhomboidalis, &c.) forming the basis of the massa intermedia of the third ventricle, and of fine medullated and non-medullated fibres which run in a subependymal position among the cells. The system links up the pars dorsalis with the pars ventralis diencephali. In dealing with the evolutionary history of this part of the brain and with the connections of the hypothalamus, reference was made to the contrasting rôles which are apparently played by the dorsal and ventral parts of the diencephalon in the psychic life of the organism. The hypothalamus, it was noted, is kept in close touch with all those visceral activities which comprise the vegetative functions of the body, and it is able to do this in virtue of its nervous connections and of its relations to the pituitary gland. It seems to be an essential element in the integration of emotional reactions and in the psychogenesis of emotional experience. While the ventral part of the diencephalon is thus essentially concerned with the internal environment of the organism, the dorsal part (which includes the thalamus proper and the epithalamus) forms an elaborate sensory correlation centre for the reception of impulses which owe their origin to changes in the external environment. It is through the pars dorsalis diencephali that the organism is enabled to develop an awareness of objective phenomena. Thus the two parts of the diencephalon seem to be primarily concerned with two contrasting aspects of conscious activity, and, as we have seen, even in the earliest type of vertebrate brain it is possible to discern in a primitive and simplified form the structural basis of this dualism of psychic life. The periventricular system of fibres and interstitial nuclei may perhaps be regarded fundamentally as a link between the dorsal and ventral parts of the diencephalon, an anatomical connection through which external stimuli may be appropriately articulated with the organic functions of the body at the diencephalic level.

If the dorso-medial nucleus is regarded in the light of these considerations, it will be realized that it occupies a significant position, forming as it does an intermediate station through which the whole periventricular system can be brought under the dominating influence of the frontal cortex of the cerebral hemisphere. In other words, the dorso-medial nucleus provides a mechanism whereby the highest functional levels of the brain are enabled to control the more primitive elements of mental activity, such as are represented in emotional reactions, instinctive impulses, &c. In this connection reference may be made to the experiments of Fulton and Ingraham [21], who, by making an incision in the prechiasmatic region of the medial surface

of the cerebral hemisphere of cats, were able to alter profoundly the emotional behaviour of the animals. It is probable that this lesion involved the course of the fibres which run from the frontal pole back to the dorso-medial nucleus of the thalamus. It is possible also, on anatomical grounds, for corticopetal impulses to reach the prefrontal areas of the cortex along the same system, so that in these areas the resultants of all the diverse activities of the cerebral cortex may be brought into close functional relation with the activities of the visceral centres of the hypothalamus. The prefrontal areas may thus be regarded as a final product of cerebral development where the activities of the purely cortical mechanisms underlying the intellectual components of personality are equated with the activities of the hypothalamic region which are associated with the more fundamental and primitive components. In this way a means is provided for harnessing the impulses which are indissolubly linked up with elementary forms of emotional experience to the intentions and resolves which have their origin in ideational processes taking place at the highest intellectual levels.

REFERENCES.

- [1] ALLEN, W. F. "Origin and Destination of the Secondary Visceral Fibres in the Guinea-pig," *Journ. Comp. Neurol.*, 1928, **35**, 275.
- [2] BREMOND, A. "Experimentell-anatomische Untersuchungen über die cortifugalen optischen Verbindungen bei Kaninchen und Affen," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1930, **129**, 65.
- [3] BROUWER, B. "Experimentell-anatomische Untersuchungen über die Projektion der Retina auf die primären Opticuszentren," *Schweiz. Arch. f. Neurol. und Psychiat.*, 1929, **13**, 118.
- [4] CAIRNEY, J. "A General Survey of the Forebrain of *Sphenodon punctatum*," *Journ. Comp. Neurol.*, 1926, **42**, 255.
- [5] CAJAL, S. R. Y. "Histologie du Système nerveux," 1911.
- [6] CLARK, W. E. LE GROS. "The Thalamus of Tupaia," *Journ. of Anatomy*, 1929, **63**, 117.
- [7] *Idem.* "The Thalamus of Tarsius," *ibid.*, 1930, **64**, 371.
- [8] *Idem.* Proceedings of the Anatomical Society, *ibid.*, 1931, **66**, 188.
- [9] *Idem.* "The Anterior Nuclei," *Brain*, 1929, **52**, 334.
- [10] *Idem.* "The Brain of *Microcebus murinus*," *Proc. Zool. Soc. Lond.*, 1931, 80.
- [11] *Idem.* "A Morphological Study of the Lateral Geniculate Body," *Brit. Journ. of Ophthalmol.*, 1932, **16**, 264.
- [12] *Idem.* "An Experimental Study of Thalamic Connections in the Rat," *Phil. Trans. Roy. Soc.* (in course of publication).
- [13] COTTELL and WILSON, "Affective Symptomatology of Disseminated Sclerosis," *Journ. Neurol. and Psychopath.*, 1926, **7**, 1.
- [14] DEJERINE, J. "Anatomie des Centres nerveux." Paris, 1901.
- [15] EDINGER, L. "Vorlesungen über den Bau der nervösen Zentralorgane des Menschen und der Tiere." Leipzig, 1908.
- [16] ELLIOT-SMITH, G. The Arris and Galé Lectures, *Lancet*, 1910, **1**, 1.
- [17] *Idem.* "The Central Nervous System." "Cunningham's Anatomy," 6th edition, 1931.
- [18] FORBES, A. "Thalamus Opticus." *Ges. Abh. München.*, 1872.

- [19] FRIEDEMANN, M. "Die Cytoarchitektonik des Zwischenhirns der Cereopitheken," *Journ. f. Psychiatr. u. Neurol.*, 1912, **18**, 308.
- [20] FULTON, J. F., and BAILEY, P. "Tumours in the Region of the Third Ventricle," *Journ. Nerv. and Ment. Dis.*, 1929, **69**, 1.
- [21] FULTON, J. F., and INGRAHAM, F. D. *Proc. Physiol. Soc.*, 1929, p. xxvii.
- [22] GLORIEUX, P. "Anatomie et Connexions thalamiques chez le Chien," *Journ. de Neurol. et de Psychiatr.*, 1929, **29**, 525.
- [23] GURDJIAN, E. S. "The Diencephalon of the Albino Rat," *Journ. Comp. Neurol.*, 1927, **38**, 1.
- [24] HEAD, H., and HOLMES, G. "Sensory Disturbances from Cerebral Lesions," *Brain*, 1912, **34**, 102.
- [25] HERRICK, C. J. "The Internal Structure of the Mid-brain and Thalamus of Neoturus," *Journ. Comp. Neurol.*, 1917, **28**, 215.
- [26] *Idem*. "Functional Factors in the Morphology of the Forebrain of Fishes." Libro en honor de S. Ramon y Cajal, 1922, vol. 1, 143.
- [27] HERRICK, C. J., and OBENCHAIN, J. "Notes on the Anatomy of a Cyclostome Brain," *Journ. Comp. Neurol.*, 1918, **25**, 685.
- [28] HINES, M. "The Brain of *Ornithorhynchus anatinus*," *Phil. Trans.*, B, 1929, **217**, 155.
- [29] HORSLEY, V., and CLARKE, R. H. "The Intrinsic Fibres of the Cerebellum, its Nuclei and Efferent Tracts," *Brain*, 1905, **28**, 18.
- [30] HUBER, G. C., and CROSSY, E. C. "On Thalamic and Tectal Nuclei and Fibre Paths in the Brain of the American Alligator," *Journ. Comp. Neurol.*, 1926, **40**, 97.
- [31] *Idem*. "Somatic and Visceral Connections of the Diencephalon," *Arch. Neurol. and Psychiatr.*, 1929, **22**, 187.
- [32] *Idem*. "The Nuclei and Fibre Paths of the Avian Diencephalon," *Journ. Comp. Neurol.*, 1929, **48**, 1.
- [33] INGVAR, S. "On Thalamic Evolution," *Acta Med. Scandin.*, 1923, **59**, 696.
- [34] JOHNSTON, J. B. "The Nervous System of Vertebrates." London, 1908.
- [35] KAPPERS, C. U. A. "Die vergleichende Anatomie des Nervensystems der Wirbelthiere und des Menschen." Haarlem, 1921.
- [36] DE LANGE, S. J. "Das Zwischenhirn und das Mittelhirn der Reptilien," *Folia Neurobiol.*, 1913, **7**, 67.
- [37] LARSELL, O. "The Nucleus Isthmi of the Frog," *Journ. Comp. Neurol.*, 1924, **36**, 309.
- [38] LOMPP, W. H. "Ueber die zentralen Opticusendigungen beim Kaninchen," *Anat. Anz.*, 1912, **40**, 309.
- [39] LÖWENSTEIN, K. "Zur Kenntnis der Faserung des Hinterhaupt- und Schäfentappens," *Abh. a. d. Hirnanat. Ins. in Zurich*, 1911, **5**, 245.
- [40] MINGAZZINI, G. "Ueber die Beteiligung beider Hirnhemisphären an der Funktion der Sprache," *Folia Neurobiol.*, 1913, **7**, 1.
- [41] MINKOWSKI, M. "Ueber den Verlauf, die Endigung und die zentrale Representation von gekreuzten und ungekreuzten Sehnervenfaseren," *Schweiz. Arch. f. Neurol. u. Psychiatr.*, 1919, **7**, 201.
- [42] *Idem*. "Étude sur les connexions anatomiques des circonvolutions rolandiques, pariétales et frontales," *ibid.*, 1924, **15**, 97.
- [43] VON MONAKOW, O. "Experimentelle und pathologisch-anatomische Untersuchungen über die Haubenregion, den Sehhügel und die Regio subthalamica," *Arch. f. Psychiatr.*, 1895, **27**, 386.
- [44] PAPERZ, J. "The Thalamic End of the Medial Fillet," *Anat. Rec.*, 1923, **25**, 146.
- [45] *Idem*. "Comparative Neurology." New York, 1929.
- [46] PAPERZ, J., and FREEMAN, G. L. "Superior Colliculi and their Fibre Connections in the Rat," *Journ. Comp. Neurol.*, 1930, **51**, 409.
- [47] PINES, J. L. "Zur Architektonik des Thalamus opticus beim Halbaffen," *Journ. f. Psychiatr. u. Neurol.*, 1927, **33**, 81.
- [48] POLJAK, S. "An Experimental Study of the Association, Callosal and Projection Fibres of the Cerebral Cortex of the Cat," *Journ. Comp. Neurol.*, 1927, **44**, 197.

- [49] POPA, G., and FIELDING, U. "A Portal Circulation from the Pituitary to the Hypothalamic Region," *Journ. of Anatomy*, 1930, **65**, 88.
- [50] PROBST, M. "Experimentelle Untersuchungen über die Schleifendigung, die Haubenbahn, das dorsale Längsbündel und die hintere Kommissur," *Arch. f. Psychiatr.*, 1900, **33**, 1.
- [51] RIESSE, W. "Beiträge zur Faseranatomie der Stammganglien," *Journ. f. Psychiatr. u. Neurol.*, 1924, **31**, 81.
- [52] RIOCH, D. M. "Studies in the Diencephalon of the Carnivora," Part I, *Journ. Comp. Neurol.*, 1929, **49**, 1.
- [53] *Idem.* "A Note on the Centre Median Nucleus of Luys," *Journ. of Anatomy*, 1931, **65**, 324.
- [54] *Idem.* "Studies on the Diencephalon of Carnivora," Part III, *Journ. Comp. Neurol.*, 1931, **53**, 819.
- [55] SACHS, E. "On the Structure and Functional Relations of the Optic Thalamus," *Brain*, 1909, **32**, 95.
- [56] TRETIKOFF, D. "Das Nervensystem von Ammonoetes. II. Gehirn," *Arch. f. Mikr. Anat.*, 1909, **74**, 686.
- [57] TSAI, O. "The Optic Tracts and Centres of the Opossum," *Journ. Comp. Neurol.*, 1925, **39**, 173.
- [58] VOGT, C. "La Myeloarchitecture du Thalamus du Cercopitheque," *Journ. f. Psychiatr. u. Neurol.*, 1909, **12**, 235.
- [59] WALLENBERG, A. "Die secundäre Bahn des sensiblen Trigemini," *Anat. Anz.*, 1896, **12**, 95.
- [60] *Idem.* "Secundäre sensible Bahnen in Gehirnstamme," *ibid.*, 1900, **18**, 81.
- [61] *Idem.* "Neue Untersuchungen über den Hirnstamme der Taube," *ibid.*, 1904, **24**, 142 and 357.
- [62] WINKLER, O. "Opera Omnia," vol. 6. Haarlem, 1921.
- [63] *Idem.* *Ibid.*, vol. 9, 1929.
- [64] WINKLER, O., and POTTER, A. "Anatomical Guide to Experimental Researches on the Cat's Brain." Amsterdam, 1914.
- [65] YOSHIDA, I. "Ueber den Ursprung der kortikipetalen Horbahn beim Kaninchen," *Folia Anatomica Japonica*, 1924, **2**, 289.
- [66] ZACHER, T. "Zur Kenntniss des Faserverlaufs im Pes Pedunculi sowie über die corticalen Beziehungen des Corpus geniculatum internum," *Arch. f. Psychiatr. u. Nervenkrank.*, 1891, **22**, 354.

NOTICES OF RECENT PUBLICATIONS.

Brain and Spinal Cord: A Manual for the Study of the Morphology and Fibre Tracts of the Central Nervous System. By EMIL VILLIGER. Edited by W. H. F. Addison. Fourth revised American Edition from the eighth to tenth German Edition. Pp. 337. J. P. Lippincott Company, Philadelphia and London. 1931. Price 25s.

It is always a pleasure to welcome a new edition of this valuable laboratory handbook, although the present edition contains few alterations from that of 1925. In the text more up-to-date descriptions of the neuroglia and of the connections of the basal ganglia are given, and several new diagrams and drawings are substituted for those in earlier editions. These changes are all for the better and it is especially pleasing to see that a good drawing of the circle of Willis has been introduced. The absence of any description of the vascular supply of the brain from almost all monographs on the anatomy of the nervous system is all the more regrettable since the descriptions given in the larger textbooks of anatomy are in most cases incomplete and even misleading. The illustrations of sections through the brain-stem make this book so valuable to the student of neurology that we should like to see it still further adapted to his needs by amplification of the sections devoted to those parts which have most clinical interest. For example, only eighteen lines are devoted to the basal ganglia and no description is given of their cell structure, although an excellent new diagram illustrates their connections. When we contrast this with the twenty pages devoted to the rhinencephalon we see the wide gulf which still separates the anatomist's point of view from that of the neurologist. We should also like to see more attention devoted to the main efferent and afferent tracts uniting the brain with the spinal cord. For example; the student is left to guess the position of the spinothalamic tract in the brain-stem; there is nothing either in the letterpress or the illustrations to help him. These may appear small omissions, but they detract seriously from the value of the book to the students of neurology for whom it is intended.

Anatomie des Menschen. von HERMANN BRAUS. Band III. Centrales Nervensystem. von Curt Elze. Berlin: Julius Springer. 1932. S. 234. Price Rm. 14.80.

Professor Curt has produced a well-balanced and lucidly written account of the gross and minute anatomy of the brain and spinal cord. The illustrations are new, abundant and for the most part excellent. Minor defects are that the account of the glia does not embody the most recent work, and that some of

the coloured diagrams of the main projection pathways are not as clear as is desirable, clarity having been sacrificed to æsthetic considerations.

A more serious objection is the inclusion of sections dealing with physiology. They are too brief to do justice to the subject, and they are in many instances not acceptable in point of accuracy. Thus the sensory cortex is divided into "centres" that are supposed to be concerned in different aspects of sensory perception; there are frequent references to the central pathways concerned with "protopathic sensibility," and an account of the speech functions that is highly conventional and artificial.

Nevertheless, if the reader will pass over these irrelevant sections, he will find a concise and readable description of the morphology of the central nervous system.

Humoral Agents in Nervous Activity. By G. H. PARKER. Pp. 79. Cambridge University Press. 1932. Price 6s.

In one of the most interesting and suggestive books on the nervous system that has appeared for some time, Dr. Parker presents a series of observations that argue in favour of a secretory activity of the nervous system. Except in a few lowly organized examples the evidence in favour of such activity is purely hypothetical, but many other phenomena and experiments discussed here bring it at least within the bounds of possibility that secretion may play a part in more complex nervous processes, possibly even in mental operations. The most definite facts have been obtained by the investigation of the chromatophores, the organs by which changes in colour can be effected; it has been found that in certain classes these are controlled by nervous, in others, by humoral influences, while in some both nervous and humoral influences play a part. There is also evidence that the nerves which act on the heart do so through secreted substances, and other muscles may be excited to activity by similar humoral substances, probably produced at the nerve terminals. The receptors may act in much the same way, an effective stimulus producing a chemical substance capable of exciting nerve-fibres. The author admits that many of his suggestions are purely hypothetical, but they present a new point of view in the investigation of nervous problems.

Intracranial Suppuration. By MILES ATKINSON. London: Jonathan Cape. 1932. Pp. 124. Price 5s.

This little monograph is offered as a guide to the general practitioner in the recognition of intracranial suppuration, and in effect may be said to deal mainly with the intracranial complications of middle-ear disease.

The pathology of the condition is clearly and briefly discussed, and there are useful chapters on the prevention of intracranial complications and on their early recognition. Perhaps the weakest feature of the book is its clinical descriptions of intracranial abscess, particularly where localizing signs are concerned. It is true that the author maintains that localizing signs are

virtually terminal phenomena, may even be absent throughout the clinical course, and that once an abscess is suspected exploratory puncture should be performed. But his account of the localizing signs characteristic of frontal, temporo-sphenoidal and cerebellar abscess is so inadequate that the reader could not possibly make a localizing diagnosis on the information provided. Thus, in the case of frontal abscess he states that while "altered disposition, moral perversion, &c.," might be expected, they do not in fact occur, and that paresis of the crossed arm is a sign to be relied on, though it may equally occur with temporo-sphenoidal abscess. His accounts of temporo-sphenoidal and cerebellar abscess are a little more satisfying.

In the circumstances it may not be surprising that the author does rely upon localizing signs. The remedy for this, however, is not random puncturing of the brain, but the study at the bedside of the signs and symptoms of focal brain lesions. The author may be assured that by this means an intracranial abscess may be localized much earlier in its history than he supposes. By reason of its defects in this respect, the book loses much of the usefulness it might otherwise have.

Maladies du Système nerveux. Par HENRI CLAUDE. Two Volumes. 2e edition. Pp. 1,568. Paris: J. B. Baillière et fils. 1932.

The second edition of this textbook has been carefully brought up to date and expanded to meet the need of the student and the practitioner. It is still characterized by direct and lucid descriptions of the symptoms of disease and by its comprehensiveness despite its relatively small bulk. It is a pity it is not more liberally illustrated and that the paper on which they are printed does not show up satisfactorily many of the pictures provided. The lack of references deprives these volumes of much of the value they would otherwise have, but they will undoubtedly be widely consulted as the presentation of the personal views of a distinguished French neurologist. There is a useful index.

Les Tumeurs du Quatrième Ventricule. Par J. LEREBoullet. Pp. 431. Paris: J. B. Baillière et fils. 1932. Price 65 francs.

The relative frequency of growths occupying or projecting into the fourth ventricle makes this monograph a valuable addition to the literature on cerebral tumours. It is based on twenty cases hitherto unpublished which were personally studied and an analysis of 320 cases collected from the literature. After a short review of the anatomy and embryology of this region the author describes the chief symptoms produced by these tumours and their value in diagnosis and localization; he lays weight on the prominence of general pressure disturbances, the occurrence of tonic seizures of the type described by Jackson, and the tendency for the cranial nerves to escape. Abnormal attitudes of the head and hypo-excitability of the labyrinths are also regarded as symptoms of value in diagnosis. The clinical and histological features of the various types of tumour found in the fourth ventricle are

then described at length; in these chapters there is an unnecessary recapitulation of symptoms discussed earlier, and the sections on histology might have been abbreviated as the author has nothing to add on the classification or nature of these growths.

Handbuch der Geisteskrankheiten. Herausgegeben von OSWALD BUMKE.

Band 11, Spez. Teil VII. S. 1,132, mit 645 zum Teil farbigen Abbildungen. Berlin: Julius Springer. 1930. Price 187.60 Rm. (mit Notnachlass Rm. 169.84).

This large and magnificent volume presents a complete picture of what is known concerning the anatomical changes in the psychoses. It is edited by Professor W. Spielmeyer, whose introduction to the book is a clearly conceived and masterly disquisition on the place and value of anatomical study in relation to mental disorders. He emphasizes that histopathological studies are here ancillary to the clinical problems of psychiatry. He deals first with the qualitative analysis of the anatomical findings and their localization; and he discusses the making of an anatomical diagnosis, the pathogenetic analysis and physiological interpretation of the findings and their application to the question of symptomatology, course and treatment as well as to the general biological aspects of the whole problem. In this last section the sobriety of Spielmeyer's wide and critical survey is especially evident.

W. Weimann writes on intoxications, including such endogenous ones as may be associated with diseases of the blood and endocrine glands. He is also responsible for the section on infections. Spatz has an exhaustive monograph on encephalitis of every kind; the distinctions between true and pseudo-encephalitis are carefully examined and the clinical significance of the anatomical findings in epidemic encephalitis set forth. Steiner writes a restrained chapter on disseminated sclerosis and Schilder's disease, which is followed by one on cerebral trauma by Neubürger and v. Braunmühl. A most comprehensive account of the changes that may be effected by syphilis in the brain occupies the next 200 pages, Franz Jahnel writing on general paralysis, and the late Professor Jakob on syphilis of the brain and its membranes. Arterio-sclerosis by K. Neubürger, senile dementia and Alzheimer's disease by E. Grunthal, and Pick's disease by v. Braunmühl, are sections in which the clinical relations are constantly borne in mind. Epilepsy is dealt with by W. Scholz, and dementia præcox briefly by H. Josephy. Schob writes a most thorough and authoritative monograph on the various conditions that may be associated with idiocy. The volume concludes with two articles by J. Hallervorden, one on extra-pyramidal disorders and the other, of notable value, on the various processes which cannot properly be included in any of the familiar categories.

This is not so much a book as a collection of monographs of the first order. Its general production and appearance is beyond cavil; this is particularly true of the excellent microphotographs and other illustrations. The indices and bibliographical lists are exhaustive.

L'Intuition délirante. Par R. TARGOWLA et J. DUBLINEAU. Paris: Maloine. 1931. Pp. 316. Price 85 fr.

This memoir is an amplified version of a paper by Dr. Dublineau which won the Prix Esquirol in 1929. It is concerned with delusional ideas which rise suddenly into consciousness, are accompanied by a feeling of immediate and absolute certainty beyond all proof or disproof, and are entirely personal. The authors do not attempt psychological analysis of this symptom but only its clinical description and study. This little book shows very well the dangers as well as the value of purely descriptive work, of which the result is commonly to make independent and significant that which is merely a particular aspect of a general psychic disturbance, to introduce fresh categories, and to present in a new light not always brighter than the old one. The discussion of intuition in general by the authors and their clinical analysis will be found informative.

La Folie au XXe Siècle. Par A. RODIET et G. HEUYER. Paris: Masson. 1931. Pp. 359. Price 40 fr.

In order to ascertain whether since the war there has been in France, and particularly in Paris, a change in the incidence and forms of mental disorder the authors have examined the records of the special infirmary which serves as a clearing house for the majority of the insane of Paris. In the event, however, the work in which this is reported becomes a textbook of French psychiatry with illustrative case histories. The third part of the book deals with the various modes of disposal and treatment, largely from the point of view of the administrator. To the question the writers set out to investigate they give a negative answer.

Psychological Factors in Peripheral Vision. By G. C. GRINDLEY. Medical Research Council Report. No. 163. London: 1931. Pp. 49. Price 1s.

Studies of the kind here described are not easily to be interpreted as yet but they furnish interesting provisional data which will doubtless contribute to the working out of the theory of perception. The author is well aware of the artificial nature of his experiments, which were concerned with the tachistoscopic exposure of various forms in the peripheral field; he draws no premature conclusions but is content to state the findings and suggest caution. He is inclined to the view that the central factors involved in peripheral form perception are not radically different from those operating in direct vision. It does not appear from the list of references that the author is acquainted at first hand with the excellent studies of the Leipzig school (Krueger, Sander, Schneider) which bear closely upon his research.

Il Processo Fine della Coscienza. By CASIMIRO FRANK. Roma: Tipografia La Precisa. 1931. Pp. 386. Price L. 50.

Like many other writers of large and ambitious books in this branch of medicine, Dr. Frank invents new words and makes extreme claims. He attempts to bring his psychological views into relation with the known structural arrangements in the cerebral cortex, but the attempted synthesis is unhappy, and the psychological views put forward will not find general acceptance. The author attributes great importance to suggestibility in normal as in morbid psychology, or as he calls it "biopsychology," and on this he bases his "biopsychotherapy" and "biopsychagogia," in which the chief work is done by "corticagogia," a verbal procedure. The author's earlier study of speech-disorders during the war has here influenced him a good deal.

Psychopathology of Forced Movements and the Oculogyric Crises of Lethargic Encephalitis. By SMITH ELY JELLIFFE. Nervous and Mental Disease Publishing Co., New York and Washington. 1932. Pp. 219. Price \$4.00.

The first half of this book is devoted to an exhaustive account of the literature of oculogyric crises. Jelliffe then reports briefly his own four cases, two of whom have been described in his earlier work on postencephalitic respiratory disorders, and passes to the psychoanalytical interpretation of the symptoms. The polemical and omnium gatherum style of this part of the monograph makes it unusually difficult to do justice to the author's attempt at explanation in terms of psychological and biological happenings. If one can accept the Freudian method of approach as being applicable to such phenomena as these, the material presented is interesting, but it is in any case associated with a rather inchoate mass of allusions to names and scientific catch-phrases. It is unfortunate that where such wide reading has gone to the making of a book it should appear to be so ill-digested.

Zur Klinik und Analyse der psychomotorischen Störung. von OTTO KAUDERS. Berlin: S. Karger. 1931. S. 132. Price Rm. 12.60.

The chief value of this phenomenological study of the motor disturbances in mental disorder lies in the protocols and the detailed, if wordy, discussion of motor processes as manifestations of the total personality. The investigation, which was largely concerned with delirious patients, showed how futile is the assumption that purely neurological or purely psychopathological explanations are adequate in this field. Although the writer has brought in more or less relevant anthropological and biological matters, the treatment is too heavy for the slender material; there is nothing particularly new or stimulating in it.

Neurobiologie de l'Hallucination. Essai sur une variété particulière de désintégration de la fonction. Par RAOUL MOURGUE.
Bruxelles: Maurice Lamertin. 1932. Pp. 416. Price 65 fr.

Dr. Mourgue has been studying the problem of hallucinations for the last fifteen years; in that time he has read an incredible number of articles and books, here listed, most of which he found unhelpful, and worked out a hypothesis for which he claims a pragmatic value, equivalent to truth. The hypothesis is based on the general biological theory propounded by himself and the late Professor v. Monakow, and there is also great indebtedness to the teaching of M. Bergson, who writes an appreciative preface to the book.

The author rejects entirely the familiar notion that hallucinations are intensified and exteriorized images, and concludes that they represent a special form of the interaction of the two spheres, of instinct and orientation. It is especially with the spatial and motor aspects of hallucination that he is concerned. Normal perception and many related problems of psychology are drawn into the argument. The work is coherent, clear, and makes no extravagant claims; it is a distinguished accession to the very few comprehensive works on this subject.

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EDITOR.

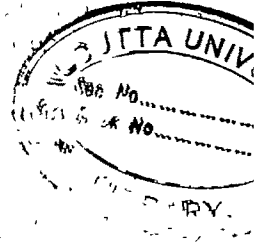
DECEMBER, 1932.

BRAIN.

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ATHETOSIS.¹

BY PAUL C. BUOY AND DOUGLAS N. BUCHANAN.



ATHETOSIS has been and still is a major subject of neurological controversy. It has been much discussed from the standpoint of associated pathology. On this aspect of the matter the present communication has little bearing and it would, therefore, seem ill-advised to reconsider at any length the well-known studies of the Vogts [13 and 14] who believe that athetoid movements are associated with lesions of the corpus striatum. Martin [7] believes that chorea, and the closely related condition of athetosis, can also be established by a lesion of the body of Luys which he considers to be the point of convergence of the striatal influence. Wilson [15 and 16], on the other hand, feels that lesions in the "cerebello-subthalamic-thalamic-cortical" afferent pathways release the effector mechanism of athetosis and of related involuntary motor activity, and he also is of the opinion that the cortico-spinal or pyramidal pathway is the central effector mechanism of athetosis. Foerster [2], on the other hand, believes that the effector mechanism is the globus pallidus which is released by lesions of the nucleus caudatus and of the putamen as shown by the Vogts. Jakob's [6] hypothesis of the patho-physiology of athetosis is essentially in agreement with that of Foerster.

Several facts are at variance with the hypothesis of the striatal origin of athetoid movements. Athetosis is associated with evidence of damage of the pyramidal system, but it has long been known that so long as the hemiplegia or quadriplegia remains complete athetosis does not develop. Not until a certain amount of voluntary movement appears in the extremity does athetosis appear. Thus it would seem that the cortico-spinal pathway is essential in the production of the

¹ From the Division of Neurology and Neuro-Surgery of the University of Chicago.

athetosis. Further clinical evidence in support of this are the observations of Horsley [4 and 5], Anschütz [1] and Payr [9], who have extirpated the portion of the pre-Rolandic gyrus related to the involved extremity and observed an immediate and permanent abolition of all athetosis, and the recently reported observation of Nasaroff [8], who injected alcohol into the motor cortex of two cases and obtained a similar abolition of these movements. The case of Spiller and Frazier [12], in which Frazier extirpated the motor cortex and obtained only a very temporary result, is so briefly reported as to be of little value in comparison with the above positive results.¹

In further support of these observations Wilson refers to Jakob's Case 18 [6]. It will be recalled that this patient with a luetic infection had a severe athetosis and subsequently developed a hemiplegia which lasted but a very few days and *then almost completely disappeared*. Nevertheless the athetosis vanished with the onset of the hemiplegia and never recurred during the patient's remaining life of eighteen months. In view of the fact that the hemiplegia was very transitory this case hardly justifies Wilson's conclusion that the athetosis disappeared because of destruction of the cortico-spinal pathway. Although the other evidence seems to support his thesis, on closer examination it becomes apparent that such may not necessarily be the case. The pyramidal (cortico-spinal) pathway which takes its origin from the giant Betz cells of the motor cortex arises from a very small part of the pre-Rolandic gyrus (Brodmann's area 4) which lies for the most part on the posterior margin of this gyrus. Thus the extirpations of Horsley, Payr and Anschütz, and the injections of alcohol by Nasaroff, must also have destroyed parts of Brodmann's area 6, or that area referred to by Foerster [3] as 6a *a* (fig. 1). By very careful and frequently repeated stimulations of the human cerebral cortex Foerster has demonstrated that area 6a *a* gives rise to two distinctly different types of motor responses. With area 4 intact, weak galvanic stimuli (stronger than those required to excite area 4) applied to area 6a *a* produce isolated movements of the fingers, the wrist, &c., similar to those obtained from area 4 itself. If on the other hand an incision of the cortex is made separating areas 4 and 6a *a*, or if the pyramidal tract has been previously destroyed, these isolated effects no longer occur. If

¹ Dr. Frazier, in a personal communication, states: "I have to-day looked up the history of the case reported and find that the craniotomy to which we referred was not performed by me, but by Dr. Edward Martin, at the Philadelphia General Hospital, some two years before I saw the patient."

under these circumstances area 6a a is stimulated with a stronger faradic current complex contralateral movements develop, such as rotation of the head and eyes, complex synergic movements of the extremities, flexion, extension, &c. As a result Foerster believes that these last mentioned motor effects are produced over an extrapyramidal system, the impulses passing from area 6a a to subcortical centres and then to the final common pathway. Anatomically there are numerous fibres from the frontal cortex, apart from area 4, to the subcortical centres. As Poliak [10] states, "Numerous corticofugal fibres

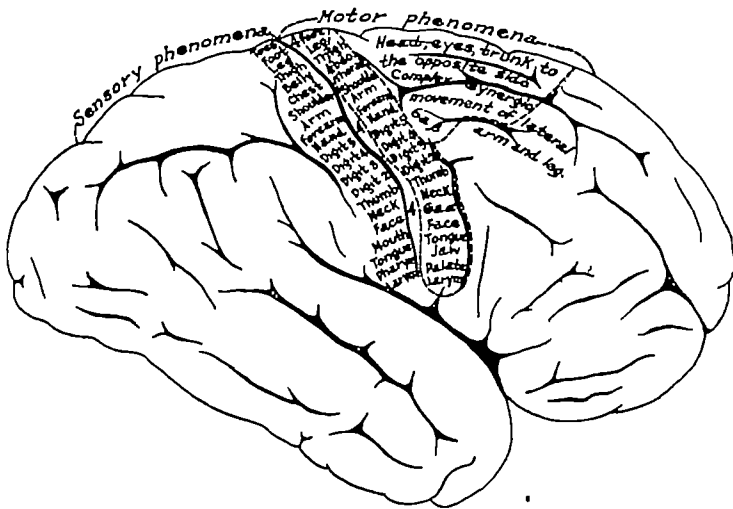


FIG. 1.—Results of stimulating the cerebral cortex according to Foerster. (Brodmann's areas 4, 6a a and 6a b have been outlined for comparison with fig. 3.)

descending from the precentral and frontal cortical regions are: (1) very numerous fibres to the caudate nucleus; (2) also numerous fibres to the globus pallidus; (3) fibres to the red nucleus; and (4) also fibres in considerable numbers to the stratum intermedium of the peduncle and to the substantia nigra; (5) besides the well known cortico-spinal, cortico-bulbar and numerous associational and callosal fibres." Thus we see that an adequate mechanism for such an extrapyramidal motor pathway as Foerster postulates exists.

Further substantiation of this thesis that athetoid movements are effected via an extrapyramidal, cortico-subcortico-spinal system, is found in the recent work of Putnam [11]. In several patients suffering from typical athetosis and dystonia he has divided the anterior columns of

the spinal cord which are generally considered to contain the reticulo-spinal and vestibulo-spinal tracts. This completely abolished all involuntary movements below the point of section *without interfering with voluntary (pyramidal) function*. This would seem conclusive evidence that some extrapyramidal pathway and not the pyramidal system is the effector mechanism of athetosis.

To recapitulate, there is much evidence to show that athetosis is effected by impulses from the cortex cerebri via an extrapyramidal motor system, and that removal of the cortex (area 6a a) or section of these extrapyramidal pathways will abolish such movements.

The following case adds further evidence in support of this conception. This young girl suffered from cerebral damage (subsequent to tonsillectomy) of undetermined nature, which resulted in a left hemiparesis, athetosis of the left arm and convulsive epileptiform attacks limited largely to the left side. The cerebral cortex was exposed and stimulated and from a definite area typical athetoid movements were produced. This area was then excised and the athetosis was never subsequently observed.

Case history.—L. N., aged 7, was admitted to the Department of Pediatrics of the University of Chicago Clinics on November 3, 1930, complaining of difficulty in using the left arm.

Past history.—The child was born at full term, with a normal delivery, and weighed 8 lbs. She was breast fed for two months and seemed to be a perfectly normal baby. She sat alone at 8 months, talked at 10 months, and walked at 12 months. She had uncomplicated whooping-cough at 4 years and chicken-pox at 5 years. During September and October, 1929, the child became pale, and started to become a mouth breather. Because of this her tonsils and adenoids were removed in January, 1930.

Present illness.—Two weeks after the operation she was sent home from school because of movements of the left arm and leg, which were "involuntary, jerky, and practically continuous." She was kept in bed for two months, and during this time the movements diminished but did not disappear. When she got out of bed after this time she limped on the left leg and held the left arm flexed at the elbow with the forearm behind her as she walked. At about this same time the child changed in character. Whereas she had always been a very good child she now began to have "temper tantrums," she became disobedient and was no longer affectionate towards her mother. Beginning in March, 1930, however, her behaviour improved and she recovered some use of her left arm, although the left leg if anything became more useless.

Examination on admission (November 3, 1930) revealed a left hemiparesis, involving the lower face, the upper and lower extremities. There was a definite resistance to passive movement in both the left arm and leg; the deep

reflexes in these limbs were all increased; the plantar response was flexor. There were typical slow sinuous athetoid movements of the left upper extremity, and the left hand was held in the typical athetoid position with the fingers hyperextended. When walking the athetoid movements were particularly prominent. The left upper extremity was in almost constant involuntary activity. Most commonly it would gradually become internally rotated and pass behind the patient. In this position it would move and jerk about in a typical purposeless athetoid manner. As she walked there was an obvious limp on the left side and she walked on the outer margin and toes of the inverted foot.

Laboratory examination at this time, which included a blood-count, blood Wassermann and Kahn reactions, and urinary analysis revealed nothing abnormal. The Mantoux test gave negative results.

During the following eleven months she was seen frequently in the outpatient department and in the hospital. The hemiparesis and athetosis continued unchanged. On January 16, 1931, she had her first convulsive seizure. She became comatose and developed clonic movements of the left side of the face, and the left arm and leg. The period of coma and convulsions lasted for five hours. She was placed upon a ketogenic diet, given bromides and luminal and her fluid intake limited. With the institution or alteration of any of these measures there was an associated period of ten to fourteen days of freedom from attacks. After this period the attacks recurred as frequently as before, although no other attack ever occurred of a duration at all comparable to the earlier. Ordinarily the attacks occurred three or four times a day, but periods in which she would have an attack every five to ten minutes were not uncommon. The vast majority of the attacks were confined to the left side, involving the arm much more than the face or leg, and in them she was very rarely unconscious. When she was unconscious the movements were usually generalized.

On May 14, 1931, an encéphalogram was made. One hundred and eight cubic centimetres of spinal fluid were withdrawn and an equal amount of air injected. Roentgenograms revealed the *left* lateral ventricle to be larger than the right, otherwise there were no abnormalities demonstrated.

In October, 1931, she was readmitted to the hospital because for some weeks previously she had been having many slight attacks each day and usually one severe major convulsion in the evening. She was again unruly, disobedient and unaffectionate, and had frequent enuresis. Physically she had a left hemiparesis with spasticity, increased deep reflexes, an extensor plantar response and wasting of the interossei muscles of the left hand. The attacks which were seen in the hospital occurred every five to ten minutes, and had a duration of from one to one and a half minutes. In them there was an initial period when she was unable to respond to questions. Then there was twitching of the orbicularis oris followed by a slow tonic contraction of the abductors of the left arm, the flexors of the forearm and the extensors of the fingers. Both legs were stiffly extended, the left foot was inverted and the toes plantar flexed. The head and eyes were turned to the left. The child did not

lose consciousness as she was able to answer questions afterwards which were put to her during the attack.

Throughout this period of observation the left arm and hand showed frequent athetoid movements in which the forearm slowly flexed; the wrist was pronated and the arm slightly abducted. Then with slow writhing movements the arm was raised and turned until the left hand was behind the head (fig. 1). Voluntary effort of the right hand or arm exaggerated all these move-

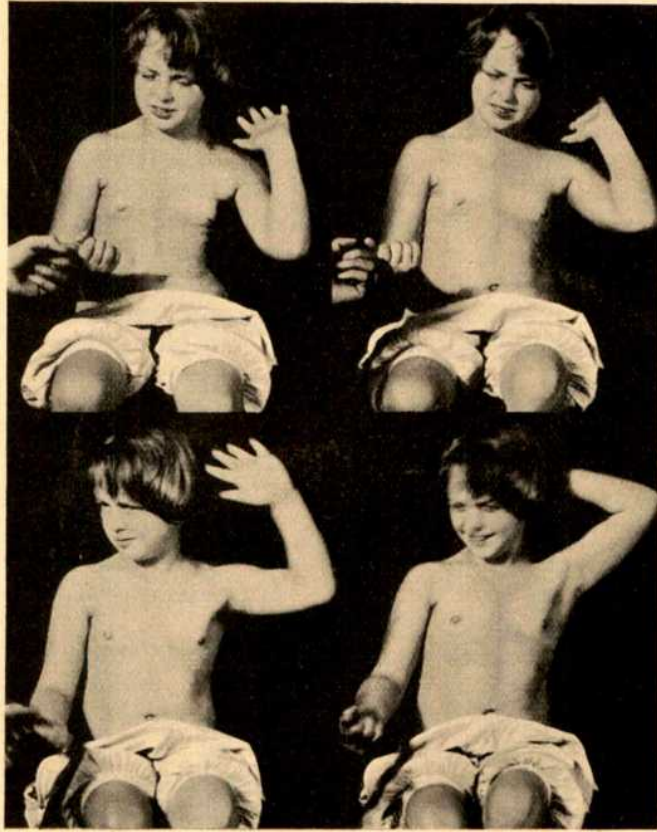


FIG. 2.—One of the types of involuntary athetoid movements which were constantly occurring in this patient. In this particular instance it has been augmented by voluntary activity of the right hand.

ments. The involuntary jerkings which this child showed during her epileptic attacks were also slow and athetoid in form, although they were distinctly different from the constant athetosis.

On October 13 a second encephalogram was made, but this revealed nothing that was not shown by the first. After it there was a period of fourteen days when the attacks were less frequent and less severe.

With the hope that we might be able to benefit the child by diminishing the frequency or severity of the convulsions she was operated upon November 5, 1931. Under ether anaesthesia an osteoplastic flap over the right posterior frontal and parietal areas was reflected, exposing the central sulcus in the middle of the operative field (fig. 3). The entire exposed cerebral cortex was stimulated by a faradic current, using a small bi-polar electrode. The current was just sufficiently strong to elicit a very weak contraction of the exposed temporal muscle. The only portion of the exposed field which was excitable was the field indicated in fig. 3. Anatomically this corresponded to the central part of the pre-Rolandic gyrus. With this relatively weak stimulus only isolated movements of the fingers and wrist of the left hand were obtained. As

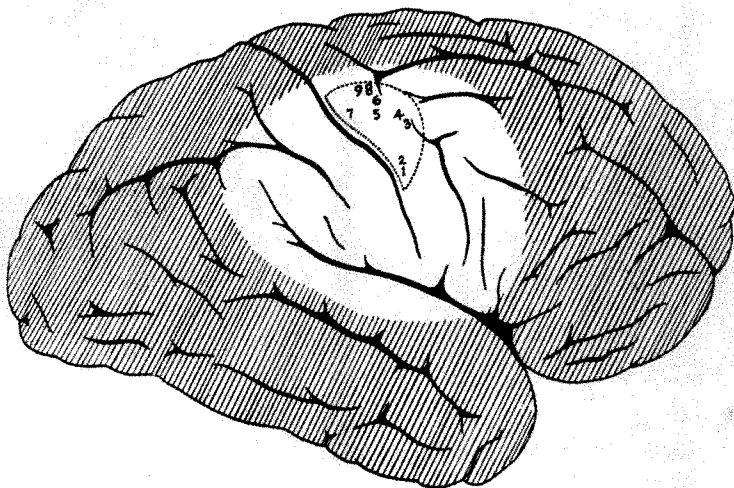


FIG. 3.—The cortex of the case reported. The clear area indicates the field exposed at operation. The zone enclosed by the broken line is the area which was extirpated down into the lateral ventricle. The figures indicate points from which positive results were obtained on stimulating the cortex. The results, all contralateral, were as follows: Using a weak faradic current: 1, flexion of the wrist laterally; 2, extension of thumb and fingers; 3, extension of wrist; 4, extension of wrist and fingers; 5, extension of wrist and fingers and flexion of elbow; 6, extension of middle finger; 7, extension of wrist and fingers. Stronger faradic current: 8, slow twisting of wrist and abduction of arm; 9, slow sinuous movement of entire arm in which the fingers were irregularly hyperextended, wrist extended, elbow flexed and entire extremity raised upward and backward.

the strength of the current was increased complex movements of the left arm appeared, identical with those involuntary athetoid movements previously observed in the patient. The wrist was pronated, the arm became flexed at the elbow, abducted at the shoulder and the entire extremity elevated upward and backward. The movement was slow and sinuous, not at all similar to the rapid convulsive movements so frequently initiated in epileptic patients by stimulation of the cortex. At no time were any movements seen in the left side of the face or in the left lower extremity. The excitable area as outlined

in fig. 3 was then excised down into the lateral ventricle. This extirpation was largely from area 6a α , removing only a very small portion of the anterior margin of area 4.

On the day following the operation she was unable to flex the left elbow, or move the left wrist or fingers; she could, however, extend the elbow and adduct the arm at the shoulder, but abduction at the shoulder was very weak. The left arm was quite flaccid. There was a slight left facial weakness, as before the operation. The left leg was not altered in any way. The movements in the left arm, which were weak immediately after operation, gradually increased in strength. A week after operation weak flexion of the elbow returned and four days later pronation and supination of the forearm.

She was discharged on November 18, 1931, and was given luminal (gm. 0.60 t.i.d.). She was unable to move the left wrist or fingers and had had no convulsive seizures.

Athetoid movements never recurred after the operation, but seventeen days after the operation the patient again had a convulsive attack. On November 30 the patient had a series of about thirty successive attacks in which the left side of the mouth twitched, the eyes turned momentarily to the left and then swept around to the mid-line position, and simultaneously extension of the left wrist, pronation of the left forearm, flexion of the elbow and abduction of the arm occurred. The fingers of the left hand did not move, nor was the left leg involved. During all of this series of attacks the patient was conscious, spoke normally after each attack and understood what was said to her during an attack.

On December 1, 1931, a third encephalogram was made. It did not differ from the previous ones and did not reveal the operative defect. After the encephalogram she had only one very slight attack on December 3, 1931, and no other during her stay in the hospital. She was discharged on December 13, 1931, with luminal gm. 0.06 t.i.d. Since then, except for one series of attacks in December with convulsive movements of the left side every three to five minutes, the number and severity of the attacks have progressively diminished, and she has had periods of over a month with no attacks at all.

When last seen on June 1, 1932, she was still having attacks. These occur in cyclic periods. She will frequently go for from ten to fourteen days without any. They then begin and increase in frequency until she has one every few minutes. The attacks then cease suddenly and will not recur for several days. They are far less severe than formerly. At first the patient will become flushed and then the musculature of the left side of the face will contract. Frequently nothing else occurs and the patient is often not aware that anything has happened. These mild attacks are so transitory that they are only seen by carefully observing the child. In the more severe attacks the movement of the face is followed by extension and internal rotation of the arm and a few flexor contractions in the leg. Clonic movements do not occur in the arm. The patient no longer loses consciousness. With these attacks the patient is often nauseated and may vomit.

Athetoid movements have never been observed since the operation. On performing voluntary movements with the right hand no movement occurs in the left. As the patient walks the left arm, which is slightly stiff, is held flexed at the elbow and moves very little. No athetoid involuntary movements such as were present before the operation have been observed since.

In spite of the very definite improvement in the attacks and the absence of the athetosis, the change in the child's character has, in the mother's opinion, become worse. To us there is little apparent change and it is not impossible that the child's great activity and disobedience have only become a greater strain upon the mother.

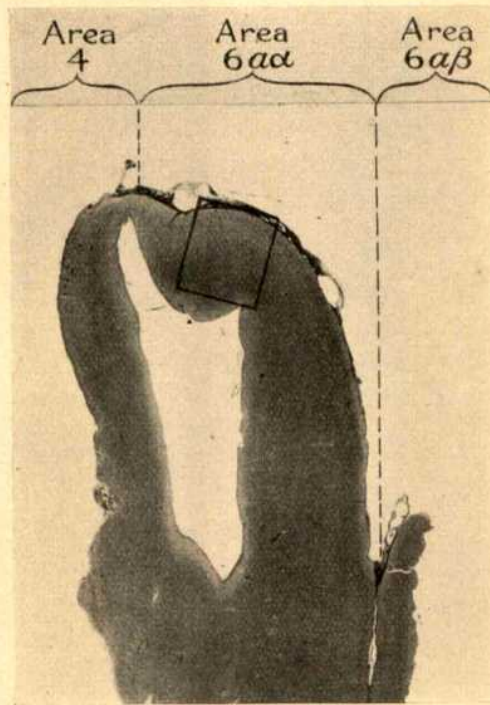


FIG. 4.—Horizontal section of the extirpated piece of cortex. The portion extending down to the ventricle is not shown. The defect in the centre of the section is an artifact. The corresponding cortical areas of Brodmann are indicated. The division between areas 4 and 6α corresponds with the microscopical findings. Hæmatoxylin and eosin, $\times 4$.

Microscopical description.—The extirpated piece of cerebrum (fig. 4) was fixed in formalin and stained or impregnated by the following methods: hæmatoxylin and eosin, cresyl violet, Perdrau's modification of Bielschowsky's reduced silver impregnation, Penfield's combined method for oligodendroglia and microglia, and Globus's modification of Cajal's gold sublimate.

Dr. Roy R. Grinker has very kindly furnished us with the following report of the findings.

The leptomeninx is definitely thickened, especially the arachnoid. There is much more reticulin in this membrane and within the loose meshes is much fresh blood. Reticulin stains reveal also a definite thickening of the blood-vessels in the grey cortex and in the superficial white matter. Several medullary vessels show in addition a moderate proliferation of the endothelial lining. Small diapedetic hæmorrhages (operative) are present in ring formation

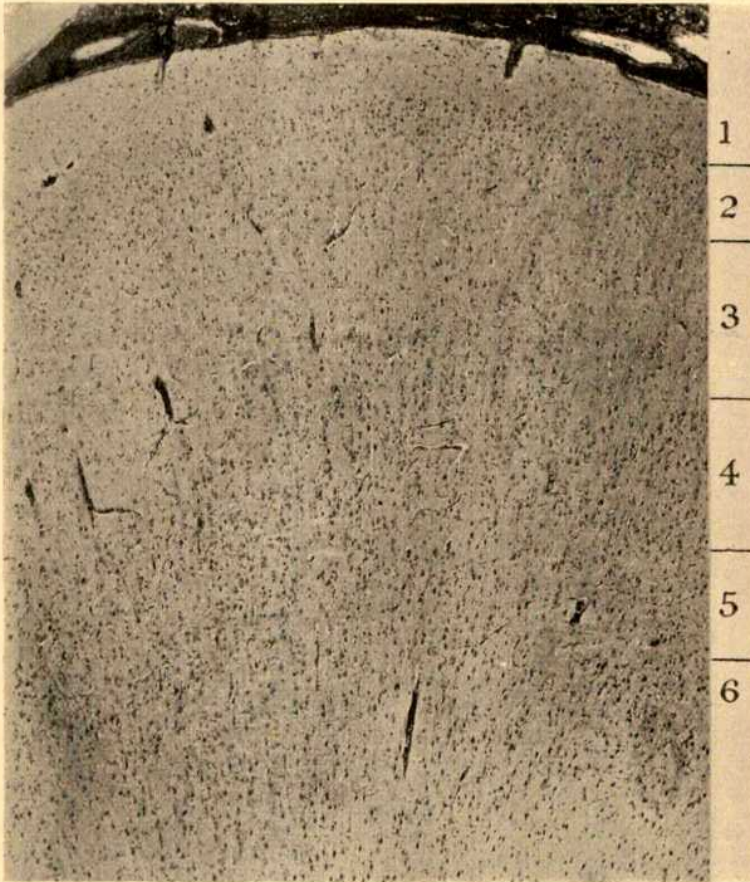


FIG. 5.—Higher magnification of area indicated in fig. 4. The thickened meninges are filled with blood due to the operation. In the upper cortical layers, particularly 3, numerous cells have disappeared, while many of those remaining are abnormal. Fairly normal moderate-sized pyramidal cells are seen in layer 4. There are, however, no giganto-pyramidal Betz cells. The layers of the cortex are indicated along the right margin. Hæmatoxylin and eosin, $\times 38$.

about the small arterioles. There are no signs of inflammatory cells nor evidences of perivascular infiltrations.

The architecture of the cortex is profoundly distorted by the fact that pathological alterations have changed the size and shape of the ganglion cells,

and many cells have completely dropped out. Of the cortical layers the first two are the only ones definitely recognizable. From a study of the size of the ganglion cells it is obvious that only one tiny bit of cortex contains Betz cells in the pyramidal layer. This area turns around a sulcus and appears to form the sloping wall of that sulcus. Continuing in the other direction the pyramidal layer contains moderately large ganglion cells but none conforming to the size of Betz cells (fig. 5).

Severe pathological alterations have taken place in the parenchymatous structures. The ganglion cells show several types of changes. The majority are swollen and rounded, their cell boundaries are uneven and irregularly frayed, the cytoplasmic mass takes an intense homogeneous blue stain in which are a few small clear spaces, the nuclear membrane is indistinguishable but the nucleolus stands out, extremely pyknotic and the processes of these cells are not clearly visible.

Other cells are also swollen and rounded and stain faintly. Their Nissl bodies have entirely disappeared. Within the cytoplasm are many vacuoles. The nucleus has become disintegrated and only a few chromatin granules are visible. Many of these cells are very faint and are "cell shadows," gradually disappearing. Another type of cell has undergone a chronic cell change. They are stained a deep blue and everything, Nissl bodies, nucleus and nucleolus, is matted together in a compact mass. These cells are narrow and angular and their deeply stained processes are visible for considerable distance but their Golgi nets are not impregnated.

The glial elements have not reacted to these parenchymatous changes. There is no increased satellitosis. There is no increase in astrocytes or definite alteration of them. The oligodendroglia in the white matter show acute swelling and increase in numbers. This change is less severe in the cortex. The microglia are moderately increased in cortex and white matter and they are somewhat plumper than normal but show no evidence of conversion into compound granular cells.

Diagnosis.—The tissue examined is compatible in its cyto-architectonics with Brodmann's areas 4 and 6. It shows severe chronic cell degeneration and a hyperplastic meningeal and vascular reaction (moderate). The changes are evidence of a slowly progressive damage on a non-inflammatory, non-vascular, possibly toxic basis.

DISCUSSION.

This case presents us with considerable information of interest. The most important is the fact that stimulation of area 6a of the exposed cerebral cortex reproduced movements identical in type with the slow sinuous athetoid movements which had so frequently been observed in the patient. The conclusion seems obvious that the cortical area from which the efferent pathway giving rise to this particular athetoid movement takes its origin, is the area 6a. This

agrees with the work of Foerster in which he has demonstrated that in the relatively normal brain complex movements of the contralateral extremity can be produced by stimulation of this same area. This, of course, at once raises the question of whether these or similar movements might not have been elicited from this same area in any patient and there is no apparent reason why this is not the case. The important fact is that the movement produced was identical with that which had so often been observed in this patient. It thus becomes apparent that in this case at least—and it is obviously fallacious to attempt to draw general conclusions from one experiment—athetoid movements identical with those observed in the patient have been produced via a mechanism which normally is capable of producing complex movements. The pathological basis for the release of this mechanism is not definitely revealed in this case. Nor have we any data which will aid us in correlating it with the lesions, striatal or otherwise, found in other cases. That in itself has no bearing upon our findings. As has so frequently been pointed out, the destructive lesion which is disclosed by anatomical study cannot possibly demonstrate to us the physiological effector mechanism which produces motor manifestations. Destructive lesions are of necessity negative phenomena. They destroy but do not produce. It is not impossible that some lesion or variety of lesions release this cortico-subcortico-spinal mechanism from higher control and thus permit it to produce athetoid movements. The proof that any one given lesion does this is not as yet forthcoming.

However, another fact is worthy of consideration. Foerster has produced complex movements from area 6a only after its connections with area 4 have been severed, or after area 4 and its efferent fibres have degenerated. Microscopic study of the tissue removed has revealed a severe degenerative process. Many neurocytes have disappeared, some others though present show pathological changes. Although it cannot be demonstrated, it is not impossible that this destruction has more severely affected the transcortical connecting fibres than it has the descending efferent pathways and thus partially severed the connection between areas 4 and 6a. If this is true, and obviously it is no more than a supposition, it is possible that the development of athetosis is permitted by degeneration of transcortical connecting pathways between these two areas, thus setting area 6a free to produce involuntarily these complex movements which it is capable of producing under artificial stimulation. This would, of course, assume that it does so in response to afferent impulses which normally play upon it.

One further point, which has considerable support in our findings, must be mentioned. The possibility exists that not only is area 6a *a* released from other control and caused by normal afferent impulses to initiate involuntary movements, but that this area may also be heightened in its irritability. On stimulating the exposed cerebral cortex in this case it will be recalled that although a large cortical area, including the postcentral gyrus (areas 1, 2 and 3), part of the superior temporal convolution (area 22) and the posterior part of the third frontal convolution (area 8), in addition to the pre-Rolandic gyrus and posterior part of the second frontal convolution (areas 4, 6a *a*, 6a *β* and 6b), was stimulated only a small part of area 6a *a* responded. It is to be assumed that the other normally excitable areas were suppressed because the patient was under ether anaesthesia, and that the remaining excitable area was excitable because it was hyper-irritable and that the degree of anaesthesia induced was not sufficient to raise its threshold above the threshold of the stimuli applied. Nothing that has been revealed in this case gives any indication of the mechanism by which such a hyper-irritability might have been produced.

Our conclusions, therefore, are that in this particular instance athetoid movements were effected from the area 6a *a* of the contralateral cerebral hemisphere which possibly was severed from its normal connections with the area gigantocellularis (area 4) and was hyper-excitable, and was put into activity by afferent impulses which normally play upon it, but which under normal circumstances would be incapable of stimulating this area to the production of involuntary movements.

SUMMARY.

(1) The case of a young girl with a hemiparesis, Jacksonian epileptiform convulsions and athetosis is presented.

(2) The contralateral cerebral cortex was exposed. Stimulation of a part of area 6a *a* reproduced movements identical with the involuntary athetoid movements observed in the patient.

(3) The area was excised, abolishing the athetosis, and subsequently the epileptiform attacks diminished in frequency and severity.

(4) Microscopic examination confirmed the fact that part of the area 6a *a* was excised as well as a very narrow strip of area 4. Definite degenerative changes were observed in the extirpated cortex.

(5) The conclusion was drawn that in this case these athetoid movements were effected by the area 6a *a*, which was heightened in irritability by some unknown process, and possibly freed from higher

(inhibitory) control by degeneration of transcortical connections, and that this area produced its effect by efferent impulses which passed via subcortical (extrapyramidal) centres to the spinal cord and the anterior horn cells.

BIBLIOGRAPHY.

- [1] ANSCHUTZ. "Hirnoperation bei Hemiathetose," *Berl. klin. Wochenschr.*, 1910, **47**, 1687.
- [2] FOERSTER, O. "Zur Analyse und Pathophysiologie der striären Bewegungstörungen," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1931, **73**, 1-169.
- [3] *Idem.* "The Cerebral Cortex in Man," *Lancet*, 1931, **2**, 309-312.
- [4] HORSLEY, V. "The Function of the So-called Motor Area of the Brain," *Brit. Med. Journ.*, 1909, **2**, 125-132.
- [5] *Idem.* "Surgery of the Central Nervous System," *ibid.*, 1890, **2**, 1286-1292.
- [6] JAKOB, A. "Die extrapyramiden Erkrankungen." Berlin, 1932.
- [7] MARTIN, J. P. "Hemichorea resulting from a Local Lesion of the Brain," *Brain*, 1927, **50**, 637-651.
- [8] NAZABOFF, N. N. "Ueber Alkoholinjektionen in die kortikale Hirnsubstanz bei Athetose," *Zentralbl. f. Chir.*, 1927, **54**, 1478-1481.
- [9] PAYR. "Case presented before the 'Medizinische Gesellschaft' at Leipzig," *Munch. med. Wochenschr.*, 1921, **68**, 1570.
- [10] POLIAK, S. "The Main Afferent Fibre Systems of the Cerebral Cortex in Primates," pp. 71 and 72. Univ. of Calif. Press, Berkeley, 1932.
- [11] PUTNAM, T. "Section of the Reticulo-spinal and Vestibulo-spinal Tracts in the Treatment of Athetosis and Dystonia." To be published in the *Trans. of the Amer. Neurol. Assoc.*, 1932.
- [12] SPILLER, W. G., FRAZIER, C. H., and VAN KAATHOVEN. "Treatment of Selected Cases of Cerebral, Spinal and Peripheral Nerve Palsies and Athetosis by Nerve Transplantation," *Amer. Journ. Med. Sci.*, 1906, **131**, 430-456.
- [13] VOGT, O. "Quelques considérations générales à propos du syndrome du corps strié," *Journ. f. Psychiatr. u. Neurol.*, 1912, **18**, 479-488.
- [14] VOGT, O. and O. "Zur Lehre der Erkrankungen der striären Systeme," *ibid.*, 1920, **25**, 627-846.
- [15] WILSON, S. A. K. "Disorders of Motility and Muscle-tone, with Especial Reference to the Corpus Striatum," *Lancet*, 1925, **2**, 215-291.
- [16] *Idem.* "Die Pathogenese der unwillkürlichen Bewegungen mit besonderer Berücksichtigung der Pathologie und Pathogenese der Chorea," *Deutsch. Zeitschr. f. Nervenheilk.*, 1929, **108**, 1-98.

THE CELL STATION OF THE VATER-PACINIAN CORPUSCLE
IN RETROPERITONEAL TISSUE. AN AFFERENT PERI-
PHERAL PATHWAY IN THE SYMPATHETIC.

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IN a previous paper [12] the main nerve-endings of the Vater-Pacinian corpuscles lying in the mesentery of the cat were shown by experiment to be terminations of nerve-fibres running in the splanchnic nerves. It is therefore reasonable to presume for the present that these fibres are afferent pathways which traverse the sympathetic nervous system.

According to our present knowledge it is now generally assumed that the cell station of all afferent sympathetic nerves is situated in the posterior spinal root ganglia. Though this is now generally accepted by most anatomists and neurologists, especially since the experimental work of Langley [4], Ranson and Billingsley [9], Rossi [11], and others, it must be remembered that the opposing view, originally supported by Dogiel [1], is still defended by a minority of neurologists. They recognize in the sympathetic mechanism, sensory neurones which belong primarily to this system, having their trophic centres in the various autonomic ganglia, their peripherally directed processes terminating in sensory nerve-endings in the viscera, and their centrally directed processes running through the rami communicantes into the spinal ganglia. Here they end by forming arborizations about special spinal ganglia cells described by Dogiel as his "Type II." Other centripetal fibres of the sensory autonomic cells are believed to end within sympathetic ganglia in connection with the dendrites of efferent cells, thus establishing a sympathetic reflex arc for the transmission of afferent visceral impulses which never rise into consciousness at all. But Dogiel's theory has not been confirmed by the many experimental researches in this field, and is now discarded by the majority in favour of the older hypothesis.

It should be mentioned for the sake of completeness that Lehmann [7], on the result of an investigation of a case of war-injury, suggested

that sensory fibres of sympathetic origin may enter the cord by anterior roots. This view is founded on one isolated case and is not confirmed by experimental work. Lebekende and Brjussowa [6], experimenting on the sensitivity of the abdominal viscera in dogs to ordinary painful stimuli, showed that section of the anterior roots had no effect on sensation.

An attempt has been made here to verify this point finally as regards the afferent nerve-fibres running in the splanchnic nerves to the Vater-Pacinian corpuscles. The problem has been approached from two aspects. First, the cells of the posterior root ganglia have been examined after section of the splanchnic nerves and evidence of degenerative changes sought for, and secondly, direct experimental proof has been brought forward, by sectioning the posterior roots either proximal or distal to the ganglia and noticing the effect in each case on the nerve termination in the Vater-Pacinian corpuscle.

For the first part of the investigation the animals used were five cats upon which bilateral division of the splanchnic nerves had been performed by the abdominal transperitoneal route. All the animals were kept for periods varying from twelve to twenty-one days and were then killed by light anæsthesia. In three of these animals a cervical, a lower dorsal (about the eighth or ninth) and a lumbar spinal ganglion were removed immediately after death, and paraffin sections made. These were stained by hæmalum and eosin in the ordinary way, and a second set of corresponding sections by Nissl's thionin blue method. The cervical and lumbar spinal ganglia were utilized as controls. From the other two animals a whole series of spinal ganglia were removed, including alternate ganglia on one side, from the first cervical down as far as the fifth lumbar. By this means it was hoped that the area, with which the afferent splanchnic fibres are associated, would be more exactly localized. These animals were killed under light anæsthesia by injection through the right common carotid artery of 10 per cent. formol solution in normal saline, in order to prevent any post-mortem shrinkage or change in the nerve-cell.

The results are seen in figs. 1 to 4. Fig. 1, taken from a section of cervical ganglion stained by hæmalum and eosin, shows the normal appearance of the spinal ganglia cells. Practically all the nuclei are centrally placed. Fig. 2 is taken from a section of a dorsal ganglion in the same animal, and stained similarly with hæmalum and eosin. The nuclei here are in many cells placed excentrically. There was no clear loss of nuclear definition, although the nucleolus was not evident in

many of them. The nuclei of the small capsular cells surrounding the neurones showed a tendency to disappear. A certain degree of shrinkage was also noticed, but as this was also to be seen in many of the other cells it was considered doubtful as an indication of degeneration. The small darkly-staining cells have been supposed by many authorities to be the cell stations of the afferent sympathetic nerves. It will be seen that these seem to show the most marked excentration of nuclei, but the change is by no means confined to these cells. Many of the larger paler-stained cells in the dorsal ganglia showed similar excentration of the nuclei after operation.

From the series of alternate ganglia removed from the same animal, this excentration of the nuclei was first noticed in the sections from the fifth dorsal ganglion. Sections from the seventh dorsal ganglion showed the most marked changes, particularly in the smaller neurones. Sections from the first lumbar showed a few isolated cells of both the large and small variety with marked excentration of the nucleus; in the rest of the lumbar ganglia the normal appearance of all the cells was again seen. The results of the Nissl stained sections were not conclusive; the same marked excentration of the nucleus in certain of the cells was again demonstrated, and in most of these cells the Nissl bodies had disappeared completely. But the appearances found were very difficult to interpret (figs. 3 and 4).

It is clear that one cannot base too much upon excentration of the nucleus alone as demonstrating degenerative changes in the nerve cell, and it was therefore decided to adopt the second method of approach by which the more direct experimental evidence could be derived.

For this part of the work, the posterior roots from the seventh to the twelfth dorsal segments on both sides of the body were divided, in one series (two animals) central to the ganglia, in another series (three animals) distal to the ganglia. Cats were used, and a laminectomy in the lower dorsal region was performed in all cases. The operation offered many technical difficulties at first, and on account of this the number of animals used in each series is unfortunately small. The results, however, are so uniform and conclusive that it was considered sufficient to establish the point in question. The animals in these cases were all left four weeks following the operation to allow complete degeneration of any nerve fibres divided from their cell stations. They were then anæsthetized and stained by the intravital methylene blue technique and portions of the mesentery prepared by the method used in the previous

investigation. In all cases the divided nerve roots were identified and confirmed on post-mortem examination.

The results obtained were both striking and convincing. In the cases where the posterior roots had been divided central to the ganglia, the nerve terminals in the Vater-Pacinian corpuscles were all stained in the usual manner. No corpuscles were found with the central axon unstained. In the second series of experiments, in which the roots had been sectioned *distal* to the ganglia, the vast majority of the corpuscles showed no nerve terminals whatever. Here and there an occasional Pacinian body would be stained in the usual manner, but they were very rare in all three animals and, further, it was found impossible to form any clear idea as to their usual orientation. They served to show that a few of the cell bodies connected with the corpuscular nerve endings in the mesentery were situated either above the level of the seventh dorsal segment or below that of the twelfth. Their presence further demonstrated the success of the method of staining in each case, and therefore the negative results could be confidently relied upon.

The afferent pathway from the corpuscles to their cell station has been shown previously to be through the splanchnic nerves.

CONCLUSIONS.

The evidence brought forward appears to fix conclusively the cell station of the Vater-Pacinian corpuscles of the mesentery of the cat in the posterior root ganglia from at least the seventh to the twelfth thoracic ganglia. The fact that a few corpuscles still stained after section of these roots distal to the ganglia suggests that the ganglion of the segment above or below this area probably also takes part in this distribution. From experiments it has been possible to trace the complete pathway of an afferent myelinated neurone from its nerve terminal in the mesentery, via the splanchnic nerves, to its cell station in a posterior spinal root ganglion.

It is, of course, debatable whether this pathway can be assigned to the afferent sympathetic system, or whether, as Gaskell [2] and Langley [5] held, all afferent nerves are part of the general nervous system, some reaching their destination along so-called somatic nerves such as the radial, some along so-called sympathetic nerves such as the splanchnics. There is no doubt that structurally there is no distinction which we can recognize dividing afferent nerves of any kind into somatic and sympathetic. Knowledge on the intraspinal and intramedullary course of the afferent impulses from the viscera which might shed some light on this question is lacking.

PLATE XIII

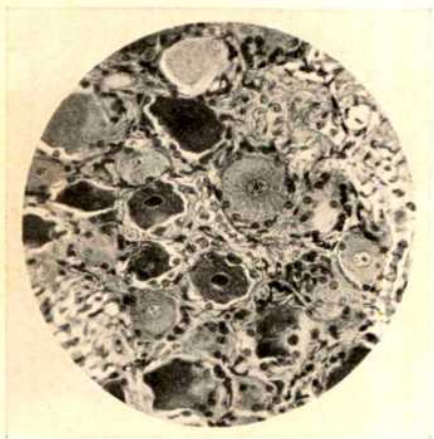


FIG. 1.

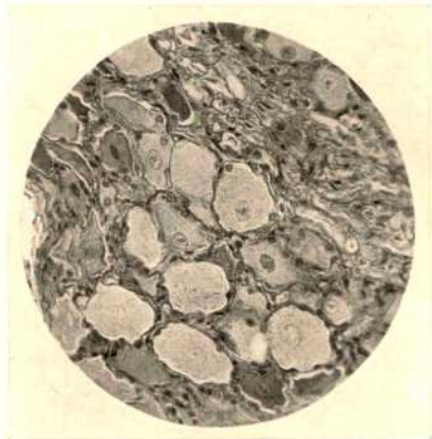


FIG. 2.

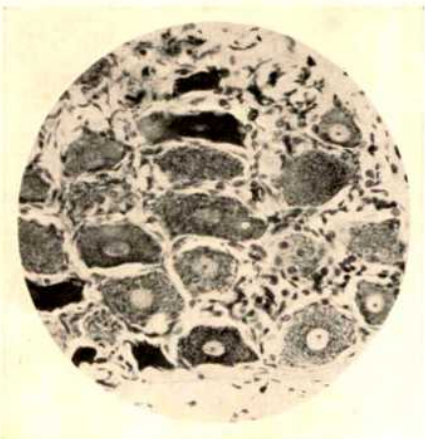


FIG. 3.

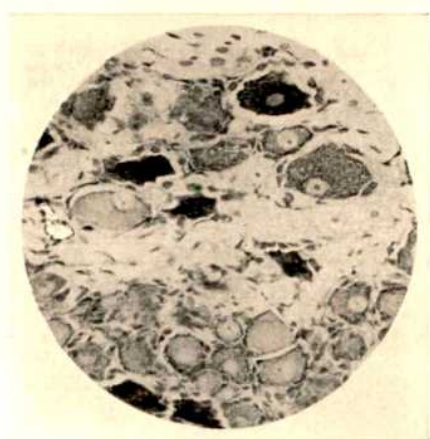


FIG. 4.

To illustrate paper by Sheehan.

But if we turn to the clinical manifestations, we find a method which apparently differentiates the two systems. Morley [8] points out there are two tests which can be applied, in so far as pain is concerned :—

(1) *The nature of the stimulus* capable of producing a painful response. The afferent splanchnic nerve fibres do *not* react to the ordinary mechanical stimuli which cause pain when applied to the surface of the body. The afferent somatic nerves, on the other hand, are sensitive to such stimuli, as cutting, tearing, burning, and the action of chemical irritants.

(2) *The character of the pain produced.* Pure visceral pain produced by stimulation of the afferent splanchnic fibres has a distinct quality, deep seated, dull and heavy in character and imperfectly localized. Pain due to stimulation of the afferent somatic nerves in the abdomen is appreciated as a more superficial sensation, is sharp or stabbing in character, and is usually accurately localized, corresponding to an area of cutaneous tenderness and muscular rigidity. By this clinical distinction Morley draws a fairly definite line of demarcation between the areas of the peritoneal cavity supplied by the splanchnic and the somatic sensory systems, e.g., the parietal peritoneum lining the abdominal cavity, the small or gastro-hepatic omentum, the mesentery and transverse mesocolon as far as an inch or so from their attachment to the bowel, and probably similarly the pelvic mesocolon, are supplied with somatic nerves; the stomach, intestines and great omentum are not. Whether this is a sufficient basis for this distinction is open to question, but it certainly appears more rational to consider the autonomic nervous system as Kuntz [3] suggests, as a functional and not an anatomical division of the general nervous system.

I wish to thank Professor J. S. B. Stopford for all the material used in this work, and for his many helpful suggestions and encouragement. The experimental work has been carried out in the Physiology Department, University of Manchester, for which facility I wish to express my gratitude to Professor Raper and Dr. Schlapp.

PLATE LEGENDS.

FIG. 1.—Section of cervical ganglion of cat. Normal appearance. Stained hæmalum and eosin. Mag. $\times 250$.

FIG. 2.—Section of thoracic ganglion of cat, following section of splanchnic nerve. Stained hæmalum and eosin. Mag. $\times 250$.

FIG. 3.—Section of cervical ganglion of cat. Normal appearance. Stained thionin blue. Mag. $\times 250$.

FIG. 4.—Section of thoracic ganglion of cat, following section of splanchnic nerve. Stained thionin blue. Mag. $\times 250$.

BIBLIOGRAPHY.

- [1] DOGIEL, S. "Zwei Arten sympathischer Nervenzellen," *Anat. Anz.*, 1896, **11**, 679.
- [2] GASKELL, W. H. "The Involuntary Nervous System." London, 1916.
- [3] KUNTZ, A. "The Autonomic Nervous System." London, 1929.
- [4] LANGLEY, J. N. "On the Nerve Cell Connection of the Splanchnic Nerve Fibres," *Journ. Physiol.*, 1896, **20**, 228.
- [5] *Idem*. "The Autonomic Nervous System." Cambridge, 1921.
- [6] LEBEKENDE, W., and BRUCSOWA, S. *Zeitschr. f. d. ges. Exp. Med.*, 1930, **71**, 198 (Phys. Abst., February, 1931.)
- [7] LEHMANN, W. *Berlin. klin. Wochenschr.*, 1920, **57**, 1318.
- [8] MORLEY, J. "Abdominal Pain." Edinburgh, 1931.
- [9] RANSON, S. W., and BILLINGSLEY, P. R. "An Experimental Analysis of the Sympathetic Trunk," *Journ. Comp. Neurol.*, 1918, **29**, 441.
- [10] RANSON, S. W. "Afferent Paths for Visceral Reflexes," *Phys. Rev.*, 1921, **1**, 477.
- [11] ROSSI, O. "On the Afferent Paths of the Sympathetic Nervous System," *Journ. Comp. Neurol.*, 1922, **34**, 493.
- [12] SHEEHAN, D. "The Afferent Nerve Supply of the Mesentery," *Journ. Anat.* Awaiting publication.

DISTORTIONS OF THE VISUAL FIELDS IN CASES OF BRAIN TUMOUR.

(*Seventh Paper.*)

THE FIELD DEFECTS AND HALLUCINATIONS PRODUCED BY
TUMOURS OF THE OCCIPITAL LOBE.

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To differentiate between tumours of the temporal and of the occipital lobes, especially when the lesion is on the right side of the brain, may frequently be difficult or impossible from the neurological studies of the patient even when dependable perimetric fields can be taken, for hemianopsia of one form or another is extremely common with lesions in either situation. The occurrence and types of field defects in temporal growths were presented in a previous paper in this series by Cushing [1] in 1921, and it is our intent herein similarly to discuss the effects characterizing occipital tumours.

Considering the importance of the occipital lobe as the "end station" for primary visual impressions, and considering the enormous number of articles which have been devoted to the injuries and the vascular degenerations of the occipital lobe, it is perhaps surprising that so little attention has been paid to tumours located there, and especially to the types of field defects which they display. Moreover, the published material is often difficult to analyse, inasmuch as both clinical studies—more especially perimetric tests—and pathological classification have been carried out in different ways.

Within recent years it has been possible to establish a correct location with much greater certainty by means of ventriculography. This procedure, however great its value, nevertheless has certain drawbacks which it would be important to overcome. Among other things, the introduction of air into the ventricles in a patient whose clinical condition is precarious may sometimes be sufficient to turn the balance from a successful to a fatal subsequently undertaken operation. In any case, though it is a minor procedure, the fact that if an intracranial

exploration is to follow a ventriculogram it should be performed on the same day, makes even more time-consuming an operation which at best may take several hours. Thus, in all probability, it will remain the ideal of the neurologist or neurological surgeon to localize a brain tumour if possible by clinical rather than by ventriculographic data. For these practical reasons, therefore, as well as for any added knowledge concerning cerebral visual phenomena, the present study has been undertaken.

Material used.—The cases upon which our investigation has been based are confined to those having purely occipital tumours as nearly as could be told by verification either at operation or at autopsy. Of these there were forty from a total of 1,881 verified intracranial tumours at the Peter Bent Brigham Hospital up to November 24, 1931. Sixteen cases of tumour extending into the temporal from the occipital lobe, and fourteen which were obviously parieto-occipital, although classed in the records as "occipital," have been discarded in order that a true picture of strictly occipital growths might be obtained. For a similar reason five cases having multiple carcinomatous metastases to the brain were discarded, as were two cases of tumour involving both occipital lobes. One patient with a single, large circumscribed metastatic nodule at the occipital pole has been included.

Of the forty patients with occipital tumours fields of vision were available in thirty, and it is therefore with this latter number that we are concerned chiefly. The remaining ten patients were either blind, comatose, or unable to cooperate because of mental disturbance.

The small percentage of occipital growths in a large verified series, as well as the comparative rarity of case reports in the literature, is doubtless explained by the fact that occipital tumours are infrequent. This might be taken to signify that their diagnosis is difficult, but while some of the histories in the present study record mistakes in localization, it seems improbable that many tumours have escaped recognition entirely in recent years. In the first place, the routine perimetric study of all patients suspected of harbouring a tumour of the brain, with repeated examination in obscure cases, would scarcely permit an involvement of the visual pathway to pass unnoticed unless the patient were already blind. In the second place, ventriculograms and exploratory operations are now performed with much greater frequency, so that patients are less likely to pass from observation with the diagnosis of "brain tumour unlocalized."

Pathological features.—Before passing to a consideration of the

visual symptomatology of occipital tumours it may be of interest to note briefly the types of tumour encountered. Of the forty growths there were twenty gliomas of one or another variety representing 50 per cent. of the total. Most numerous among these were thirteen cases of glioblastoma multiforme. It is interesting that fibrillary astrocytomas were encountered twice only, although in other brain areas they are about as common as the glioblastomas. Meningiomas were revealed in fourteen instances or 35 per cent., the remaining 15 per cent. being composed of two angiomas, one metastatic carcinoma, one hydatid cyst, and two unclassified tumours. The percentage of meningiomas might well be thought to be extremely high compared to the figure of 13·4 per cent. in a large verified series of intracranial growths as presented recently by Cushing [2]. It must be remembered, however, that in his large series are included such tumours as pituitary adenomas, craniopharyngiomas and acoustic neuromas—lesions which do not occur in the cerebral hemispheres; therefore if these were eliminated the percentage of meningiomas would rise very perceptibly.

It is difficult to compare these statistics with those of the fifty odd cases gathered by Wilbrand and Saenger [3] in 1917. For the most part the older cases are reported as sarcomas of various types, but it is not safe to assume that all of them represent mesodermal growths. The only other occipital series of considerable size in which statistics are given as to the types of tumour is the group of forty cases collected by Allen [4] in 1930, from the National Hospital, London. Of these there were sixteen gliomas of one form or another, four meningiomas, three sarcomas, two gummas, two cysts, and one angioma. In the remaining twelve the nature of the growth was not recorded.

Visual field defects.—As denoted in the title, our interest has centred upon the perimetric and hallucinatory effects produced by occipital tumours, and in view of this it may be well to recall what the studies of others have revealed concerning these features. Some form of homonymous field defect has long been known to be a frequent clinical finding in cases of tumours in one or the other occipital lobe. Nine of the fifteen occipital tumours collected by Duret [5] in 1905 showed contralateral hemianopsia, but no further details were given. Complete hemianopsia appears to have been the rule in the cases collected by Wilbrand and Saenger in the monograph mentioned above, although too much weight must not be laid on the perimetric fields in their rather miscellaneous group. Often no fields are given with the case reports, and often they are unsatisfactory. In only three instances does the

summary state definitely that the macula was spared, and in only four more was there a sector defect.

More recently (1929) Frazier and Waggoner [6] reviewed a series of forty occipital tumours, in nine of which the lesion was, however, primarily temporal and invaded the adjacent occipital lobe. The statements concerning hemianopsia in this article are of a general rather than a specific character. It is said, however, that none of the cases bore out the conception that occipital hemianopsia is less clear cut than that of lesions further forward. The authors conclude that hemianopsia and visual hallucinations are the most constant and valuable of all symptoms relating to occipital lobe tumours, their value being enhanced when in association with other symptoms.

In a recent comprehensive survey Allen, in the article already mentioned, has made an exhaustive and highly valuable study of the clinical symptomatology produced by forty tumours which involved the occipital lobe, and submits also a thorough review of the literature upon the subject. Of his total number of tumours twenty-four were confined entirely to the occipital lobe, whereas the other sixteen involved adjacent portions of either temporal or parietal lobes. Homonymous visual defects were found to be present in all but two of the patients in whom it was possible to chart the fields. As to the type of defect he outlines the following groups:—

“(a) Those with complete contralateral homonymous hemianopsia extending right up to the fixation point.

(b) Those with incomplete contralateral homonymous hemianopsia extending to the middle line above and below the field for central vision but leaving the latter more or less unaffected.

(c) Those in which there was a contralateral homonymous crescentic defect of the visual fields.

(d) Those in which there was contralateral homonymous quadrantic defect.

(e) Those in which the visual fields were normal.”

Inasmuch as Allen has outlined these groupings of the various types of field defects which may be expected in patients with tumours involving the occipital lobes it would be interesting for the sake of comparison to divide our series in the same manner. The two series, however, are not strictly comparable, since Allen included occipito-temporal and occipito-parietal growths, and though such comparisons as can be made will be referred to subsequently, we have chosen to point out primarily certain features of the hemianopic defects which we believe to be most important in the differential diagnosis of purely occipital tumours.

It has long been an impression in this clinic, as perhaps in others, that in patients showing homonymous contralateral field defects the macular fibres were likely to be spared if the tumour was occipital, whereas in temporal lobe tumours which caused a complete rather than a quadrantal defect the line would extend more often directly through the fixation point. To substantiate or to dispel this impression the fields of all patients in the present series showing such a relatively complete homonymous hemianopsia were examined primarily as to this point. In this, as in all other determinations and calculations, it is of course to be understood that the fields are those taken prior to operation. Charts of some of the fields taken after operation will be given at times as a matter of interest. The impression referred to seems to have been borne out very clearly in our investigation, since of the nineteen patients having fields in this category fourteen or 73·6 per cent. showed a distinct sparing of the macular fibres, while in five, or 26·4 per cent., there was bisection of the fixation point.

The second striking feature, which came out in looking at the series as a whole, related to the homonymous quadrantic defects. Four patients showed a clear-cut, complete loss of vision of the whole or nearly whole contralateral lower quadrants of both eyes, and one other showed this complete quadrant loss in one eye, the other being blind. In no instance was there found an example of an upper quadrantic homonymous defect, either partial or complete, a type of field which is frequently present in temporal lobe tumours.

Having determined these primary points the proposed comparison with Allen's series may be given, using his classification of field defects already cited. It must be kept clearly in mind, however, that sixteen of Allen's forty cases involved neighbouring portions of temporal or parietal lobes, whereas the cases in our series were selected on the basis of the tumour being confined to the occipital lobe. Furthermore, Allen calculates percentages from his total forty cases although fields were not available in 20 per cent. of them. For purposes of this comparison, therefore, we likewise have calculated from our total forty, fields not being available in 25 per cent.

In his first group Allen placed those cases which showed "complete contralateral homonymous hemianopsia extending right up to the fixation point," in other words, cases in which the macular fibres were bisected together with complete hemianopsia of the peripheral fields. This group was represented by 32·5 per cent. of his cases, whereas in ours the figure is 12·5 per cent. Our percentage therefore is less than

half of that found by Allen, and it is our feeling that the discrepancy is due to our exclusion of the cases in which there was extension of growth outside the occipital area, particularly in this class, the occipito-temporal tumours.

The second group to be considered is that having a complete contralateral homonymous hemianopsia except just around the fixation point. These cases represented 22·5 per cent. in Allen's series and 35 per cent. in ours. We conclude that our higher percentage in this group is because the macular fibres are more frequently spared in purely occipital tumours.

The third group comprises those cases showing a contralateral homonymous crescentic defect. Of Allen's patients 7·5 per cent. showed this type of field, whereas our figure was 5 per cent.

In the fourth category Allen designated those having a contralateral homonymous quadrantic defect, and placed 12·5 per cent. of his cases in this group. Curiously enough, the percentage figure was identical in our series.

Finally, the group showing normal fields was represented by 5 per cent. in Allen's series and again our figure was the same. It should be added that two other cases (5 per cent.) in our series could not be included in any of these groups, since sparing or bisection of the macula could not be determined from the charts.

	<i>Allen's series</i> Percentages calculated from total forty cases. Fields not available in 20 per cent.	<i>Present series</i> Percentages calculated from total forty cases. Fields not available in 25 per cent.	<i>Present series</i> Percentages calculated from the thirty cases in which fields were available
<i>Group I.</i> Complete hemianopsia with bisection of the macula	32·5	12·5	16·7
<i>Group II.</i> Complete hemianop- sia except for sparing of the macula	22·5	35·0	46·7
<i>Group III.</i> Hemianopic cres- centic defect	7·5	5·0	6·6
<i>Group IV.</i> Homonymous quad- rantic defect	12·5	12·5	16·7
<i>Group V.</i> Normal fields ..	5·0	5·0	6·6
<i>Group VI.</i> Indeterminate ...	0·0	5·0	6·7
<i>Group VII.</i> No fields available	20·0	25·0	0·0
Totals ..	100·0	100·0	100·0

In order to bring out this comparison more clearly we have put it in the form of a table. Included in the table also are the percentage figures for our own series based on a calculation from the thirty patients in whom fields were available, since for the purposes of this paper such a basis seemed more appropriate.

In order to throw further light upon the point of sparing the macular bundle the series was divided into three groups according to their pathology: namely Group I, meningiomas (fourteen); Group II, glioblastomas (thirteen); Group III, miscellaneous (thirteen), including all other types.

Group I (Meningiomas).—In this group, in which the tumour was in almost every instance circumscribed and likely to be situated more nearly at the occipital pole than in either of the other groups, there were fourteen cases. In one the fields were indeterminate, in another they were normal, while a third patient was blind. Of the eleven remaining who had homonymous field defects, nine (82 per cent.) showed sparing of central vision and in two (18 per cent.) the fixation point was bisected.

Almost without exception in this group the patients who showed intact macular fibres had, as might be expected, normal visual acuity, and their fields fell into two distinct categories, namely, a straight homonymous hemianopsia except just around the fixation point, or else a well-marked lower homonymous quadrantic defect.

The following case exemplifies well the usual findings in the former of these groupings:—

Case 1.—C. E. C., a man aged 28 (surgical number 32961), was referred to the Peter Bent Brigham Hospital on December 31, 1928, by Dr. S. M. Pearl of Boston. His family and past history were irrelevant.

Present illness: Seven months before admission the patient was awakened by a severe headache, accompanied by vomiting. This headache continued severely for three days and during this time he was unsteady in walking. Headache of moderate grade persisted until about September, 1928, and during this time he became aware that he could not see objects on his left side. During September his headache ceased and he returned to work, but vision toward the left became more and more impaired. In December, 1928, his headache returned severely and persisted until his admission.

Neurological examination revealed merely early bilateral choked discs, fine nystagmus to right and left, and the left homonymous hemianopsia as shown by the fields in fig. 1. X-rays of the skull gave no localizing evidence.

The usual question arose as to whether we were dealing with a temporal or an occipital tumour on the right side, and recourse was had to ventriculography. This procedure was carried out on January 10, 1929, and showed defective filling of the right occipital horn, together with displacement of the lateral and third ventricles to the left.

Operation was performed the same day as the ventriculogram. A right occipital bone flap was reflected with the patient in the face-down position. A large meningioma (130 grm.) was disclosed and enucleated. Its attachment was found to be along the upper surface of the tentorium and this area was carefully charred by electro-coagulation.

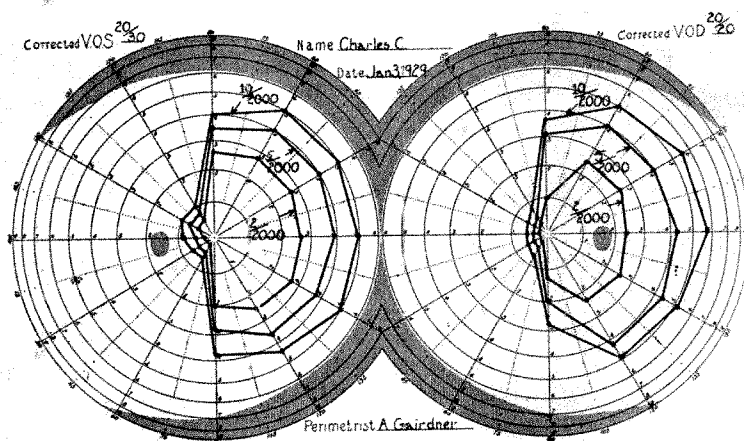


FIG. 1 (Case 1).—Pre-operative fields (screen method only) showing sparing of the macula in an otherwise practically complete hemianopsia.

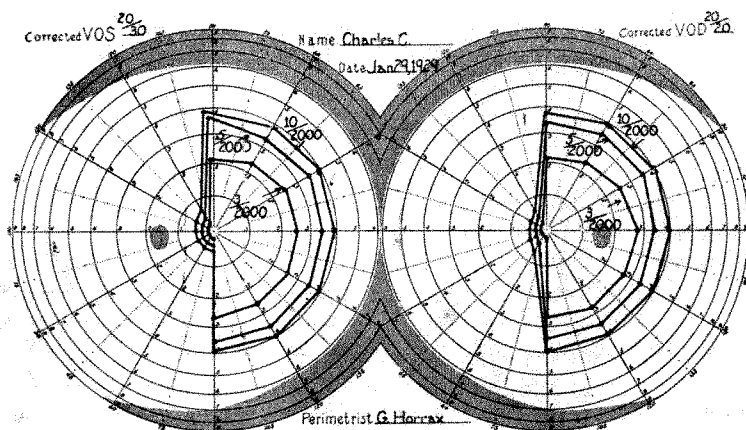


FIG. 2 (Case 1).—Post-operative fields (screen) showing little change from the configuration before operation.

The patient made an uneventful convalescence. Fields taken twenty days after operation showed the same general configuration as before (fig. 2), and he was discharged on January 30, 1929.

No special comment need be made as to any features of the above case except that in the days before ventriculography the tumour almost certainly would have been missed using the ordinary type of temporo-occipital flap.

The next case is an example of lower quadrantic homonymous defect with return to nearly normal fields after operation.

Case 2.—F. K., a young woman, aged 28 (surgical number 37217), was referred on September 3, 1930, by Dr. R. F. Loeb, of New York. Again the family and past history were irrelevant.

Present illness: For six months before admission she had had daily morning frontal headaches. These did not last long and were followed by a few moments

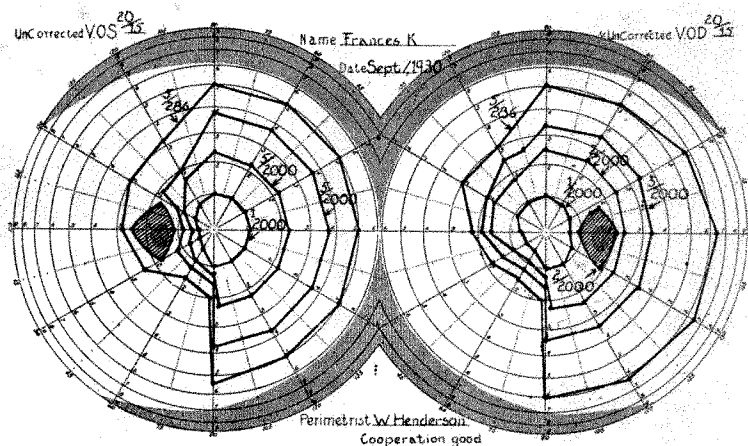


FIG. 3 (*Case 2*).—Pre-operative fields to illustrate nearly complete lower homonymous quadrantic defects (screen and perimeter).

of dizziness. Two weeks before admission her headaches became severe, constant and generalized. She also complained of some stiffness in the neck and slight numbness of the left side of the face at times. One month before admission she began to run into objects on her left side. This persisted and became troublesome and was associated with some blurring of vision and difficulty in focusing.

Neurological examination revealed bilateral choked discs of 6 diopters, some suboccipital and cervical tenderness and the left lower quadrantal field defects as shown in the chart (fig. 3). X-rays of the skull were negative.

Again being unable to tell whether interruption of the visual pathway had occurred in the temporal or the occipital lobe, a ventriculogram was performed on September 8, 1930. This showed a downward and forward displacement of the right occipital horn, together with shifting of both lateral and third ventricles toward the left.

Operation followed ventriculography on the same day. An occipital bone flap was turned down and a 170-grm. meningioma enucleated from the pole of the right occipital lobe. The patient made an easy convalescence. Her choked discs receded promptly to 1 diopter at the time of her discharge on September 29, 1930, and her post-operative visual fields showed great improvement (fig. 4).

The two patients in this group showing bisection of the macular fibres likewise had sharply cut fields, one of them hemianopic, the other a complete lower quadrantanopsia. In the former it is interesting to note that fields taken four years after his tumour was removed showed

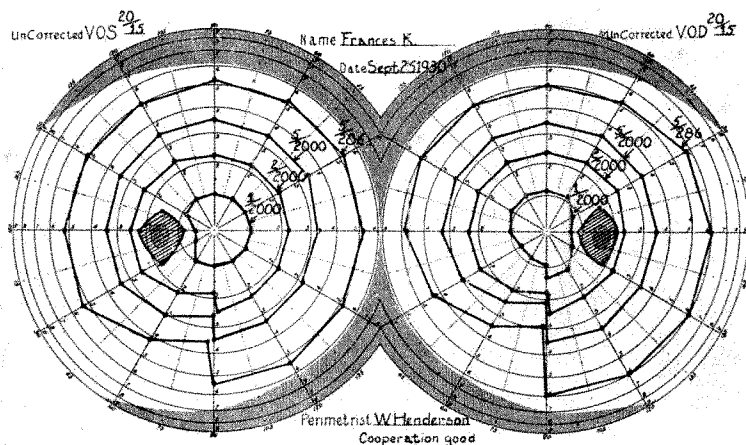


FIG. 4 (Case 2).—Post-operative fields which show great improvement after tumour removal (screen and perimeter).

that the macular fibres were intact. The record of the latter is as follows. It will be seen that this patient was one of the few in the series having visual hallucinations of the unformed type, a topic which will be touched upon later.

Case 3.—J. H. I., a man, aged 31 (surgical number 36582), was referred on May 28, 1930, by Dr. J. R. Anderson of Melbourne, Australia. Aside from a family history containing some evidence of tuberculosis, both this and his past history were unimportant.

His present illness started two and a half years before admission, at which time he began seeing spots of light toward his left side. These spots would start near the midline and work toward the left, expanding and changing in colour as they moved. The spots would be seen with the eyes either open or closed. He would see them at varying intervals of a few days or of three to four weeks, and they continued until about November, 1929, at which time they ceased completely. This patient also had generalized headaches for two

and a half years, and these persisted to the time of admission. Since November, 1929, he had noticed increasing blindness toward his left side, although this was somewhat improved after an exploratory craniotomy with decompression in January, 1930.

Neurological examination showed bilateral chronic choked discs with very slight elevation, a bulging occipital decompression and a left lower quadrantal homonymous field defect (fig. 5).

First stage operation, June 9, 1930. On this date the bulging occipital skin flap was reflected and a highly vascular meningioma partially removed.

Second stage operation, June 16, 1930. At this session the remaining portion of tumour at the occipital pole was extirpated.

The patient made a rapid convalescence and was discharged on July 2, 1930. His fields of vision after operation were essentially unchanged.

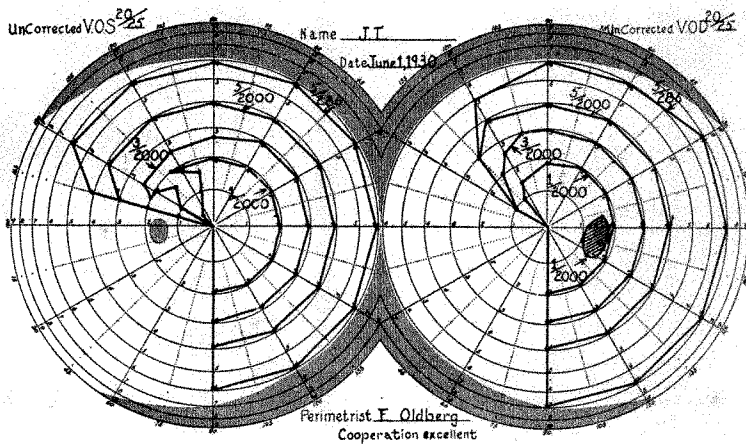


FIG. 5 (Case 3).—Pre-operative fields to illustrate complete lower quadrantanopsia with bisection of the macula (screen and perimeter).

Group II. (Glioblastomas.)—This group, in which the lesion was likely to spread widely, was represented by thirteen cases. The striking feature about them clinically was that of the total number in only six could fields be recorded, as the remaining seven were comatose or otherwise incapable of cooperation. One patient showed normal fields, and of the five others in three (60 per cent.) the macular fibres were spared, and in two (40 per cent.) they were bisected.

In the following example of those showing spared central fibres, the perimeter fields were similar to Allen's crescentic type of hemianopsia, but on the screen the line was entirely upon the vertical meridian except just around the fixation point.

Case 4.—J. L. T., a man, aged 42 (surgical number 32834), was referred on December 10, 1928, by Dr. D. B. Jewett, of Rochester, N.Y. He gave a history of untreated luetic and Neisserian infections at age 20; otherwise there was nothing of importance.

His present illness was of extremely short duration and consisted solely in his having had a sudden headache four weeks before admission, this headache having persisted until he came to the hospital, but not so intensely as when it first came on.

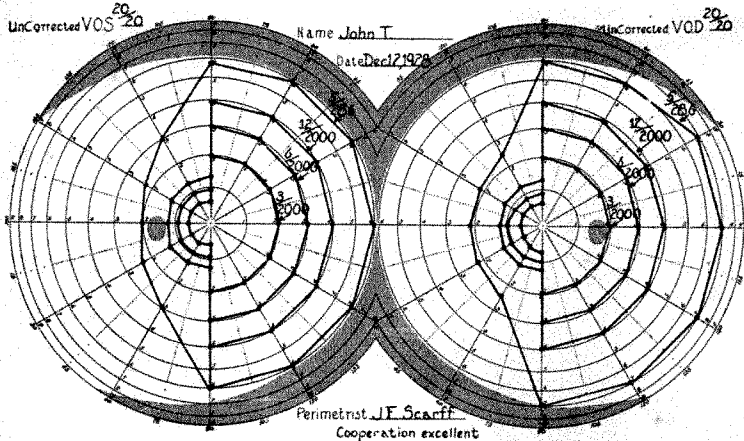


FIG. 6 (*Case 4.*)—Pre-operative fields. Straight line hemianopsia with spared macula by screen; defect somewhat crescentic by perimeter.

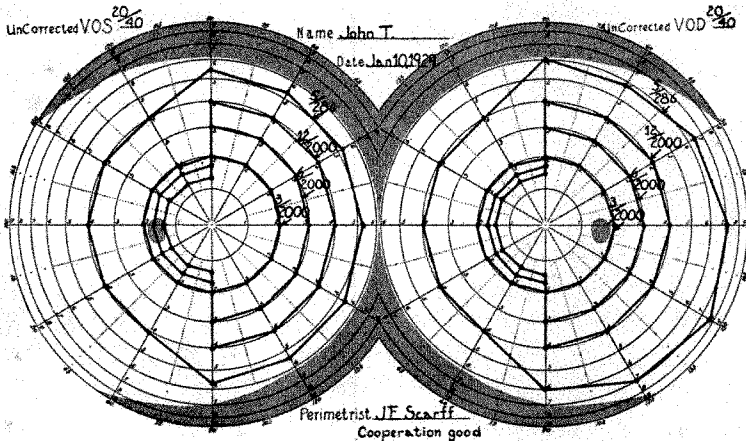


FIG. 7 (*Case 4.*)—Post-operative fields showing improvement both on screen and on perimeter.

Neurological examination showed some inconspicuous nystagmus to the right, a low grade of choked discs, more marked in the left eye, where there was an elevation of about 1 diopter, and a left homonymous hemianopsia with sparing of the macular fibres (fig. 6).

Although our impression was that this was an occipital tumour, a preliminary tap in the right occipital region was made. A gliomatous cyst was encountered, and operation followed immediately.

Operation: December 24, 1928. The usual occipital bone flap was reflected. A soft, partly cystic glioblastoma of the right occipital lobe was disclosed and extirpated as radically as possible. Although large, the growth was confined to the occipital region entirely.

The patient made an excellent postoperative recovery, and was discharged to his home on January 12, 1929. Fields taken two days before discharge showed definite widening out on the hemianopic sides (fig. 7).

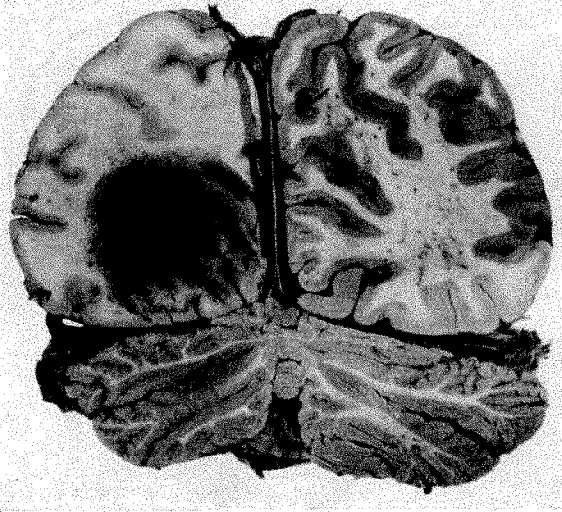


FIG. 8.—Small glioblastoma at occipital pole causing homonymous hemianopsia with spared macula.

Comment.—One of the other two patients in this group showing spared macular fibres had a medium-sized tumour in the upper, outer part of the occipital lobe; the remaining one had a small, low, mesially situated growth at the occipital pole (fig. 8). It is of some interest that this last patient had had episodes which resembled hallucinations of taste and smell, although they were hardly definite enough to be truly classed as such.

In none of the patients in this group, whether with spared or unsparing central vision, was there any tendency to quadrantal defects which seem more characteristic of circumscribed growths.

In both patients who showed bisection of the macula the tumour was of extremely large size, in each instance extending almost far

enough forward to be classed as temporo-occipital, but nevertheless they have been included. It is interesting, however, that even in one of these the macular fibres became definitely spared after operation. The record of this case follows:—

Case 5.—S. P. H., a man, aged 57 (surgical number 36700), was referred on June 15, 1930, by Dr. C. E. Guthrie of Seattle, Washington. Nothing of importance was revealed by the family and past history.

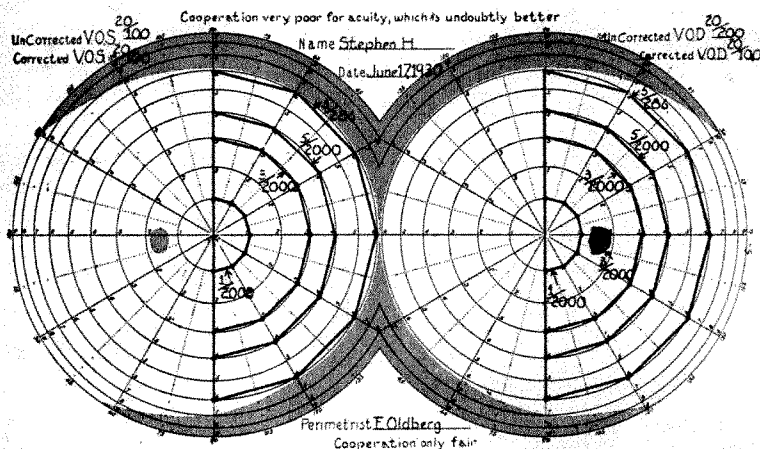


FIG. 9 (*Case 5*).—Pre-operative fields showing bisected macula (screen and perimeter).

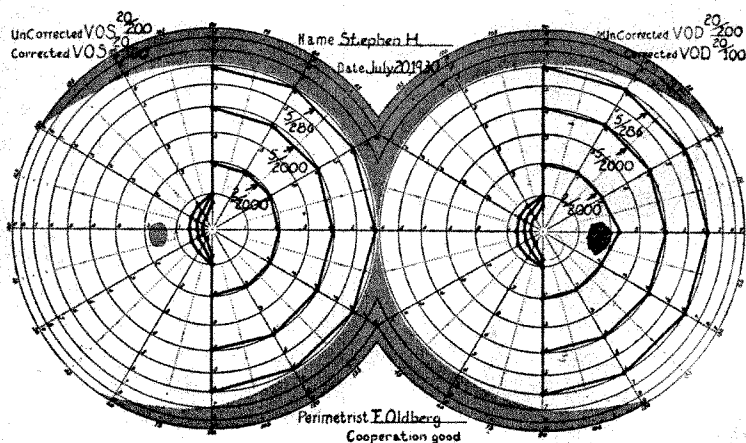


FIG. 10 (*Case 5*).—Post-operative fields in which the macula is definitely spared probably due to better co-operation (screen and perimeter).

His present illness began some six weeks before admission to the hospital with persistent blurring of vision, accompanied by gradual impairment in mental acuity. It should be said that two weeks previous to these symptoms

he had received a sharp blow in the occipital region, but this was not sufficient to render him unconscious. For about ten days before admission he had had moderately severe headaches situated in the postorbital region.

Neurological examination revealed slight left lower facial weakness, absent superficial reflexes on the left side, normal fundi and complete left homonymous hemianopsia (fig. 9). X-rays gave no indication of the tumour's situation.

A ventriculogram was carried out on June 19, 1930, and this disclosed displacement of both lateral and third ventricles to the left, with forward and upward dislocation of the right occipital horn.

Operation on this patient was delayed until the following day, June 20. On this date an occipital flap was reflected with the patient lying face down. A highly vascular, soft glioblastoma was encountered and radically extirpated by suction and by electro-surgical methods.

The patient made a good convalescence. Postoperative fields on July 20 (fig. 10) showed definite sparing of the macular fibres, whereas these had apparently been bisected before operation.

Group III. (Miscellaneous.)—The tumours in this group represented a wide variety, but on the whole they were considerably more circumscribed than the glioblastomas. The total number of patients in this group was thirteen, but in two no fields were available, and in two others who showed homonymous defects the charts were indeterminate as to whether the macula was spared or bisected. Of the nine remaining, seven (78 per cent.) showed wholly intact macular fibres, and in two (22 per cent.) the macula was bisected.

Two of the patients with spared macular bundles showed fields which were rather of the crescentic type of Allen but with distinct tendency to a lower quadrantal homonymous defect, and one showed a clear-cut lower quadrantanopsia. The others corresponded largely to the type exhibited by the following case:—

Case 6.—C. S., a housewife, aged 54 (surgical number 27915), was referred on January 3, 1927, by Dr. L. Myers of Hollywood, California. Her family and past history were irrelevant.

Present illness: During the year before admission she had had three convulsions which were without localizing phenomena. Six months before entrance she began having severe headaches with vomiting. Her sight failed progressively and she had occasional attacks of numbness and weakness of the right hand. For one month she had had difficulty in counting.

Neurological examination, as in a large proportion of cases in the series, revealed merely bilateral choked discs of $1\frac{1}{2}$ diopters, possibly slight weakness of the right hand, and the right homonymous hemianopsia with spared maculae shown in fig. 11.

After a left subtemporal decompression on January 18, ventriculograms

were made on January 26. These showed a marked concave defect in the left occipital horn, suggesting the outline of a tumour. It is also to be noted that after the decompression she had a single vague hallucination of "some one standing in the doorway" on her right side.

Operation was performed the same day. The usual face-down position was employed and a left occipital bone flap reflected. A large, firm, rubbery

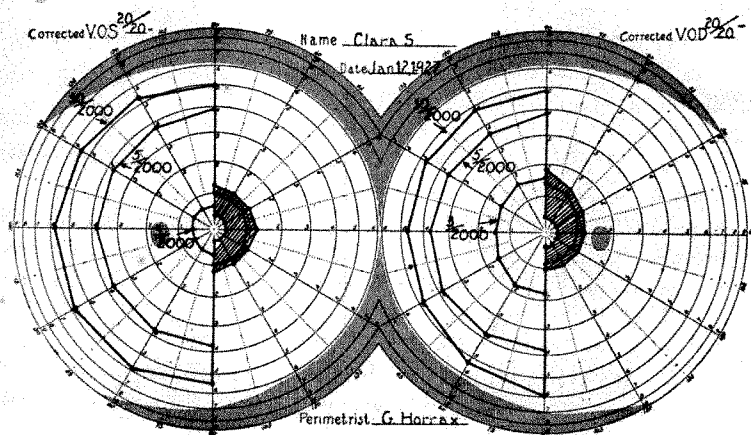


FIG. 11 (Case 6).—Pre-operative fields (screen only). Shaded area in right halves means lessened perceptibility.

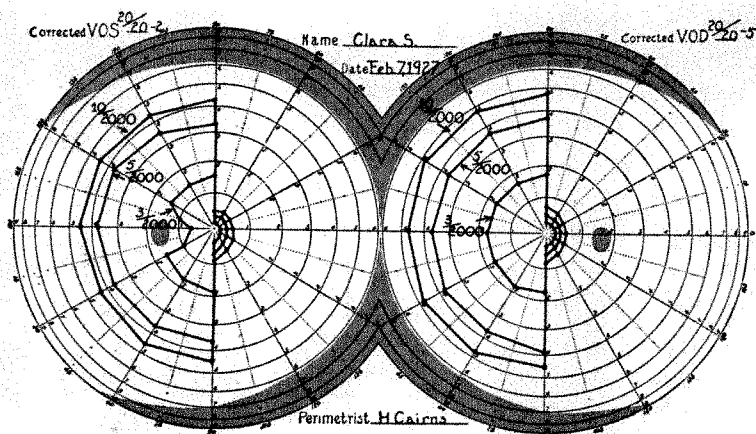


FIG. 12 (Case 6).—Post-operative fields which are not greatly changed (screen only).

tumour was encountered 3 cm. below the surface of the occipital pole, and was extirpated radically. It proved to be an astrocytoma fibrillare.

The patient did extremely well after operation although having a little temporary difficulty in reading, writing and remembering names. She was discharged on February 7, 1927, at which time her fields still showed a

distinct sparing of the maculae (fig. 12), the area around the fixation point being somewhat less than before her tumour had been removed.

Comment.—The only other fibrillary astrocytoma case in the series was a patient in coma who died without operation.

As mentioned above, two patients in this group had homonymous field defects of somewhat crescentic form, but nevertheless suggesting the lower quadrantal type. The following record illustrates this tendency as well as a slight indentation suggesting a horizontal sector defect.

Case 7.—K. D., a man aged 36 (surgical number 22172), was referred on November 9, 1919, by Dr. B. C. Frazier of Louisville, Ky.

For three months before admission he had been having headaches, vomiting, and failing vision. Neurological examination showed bilateral choked discs of 4 diopters, a right facial weakness, visual sensory aphasia and the right homonymous field defects shown in fig. 13.

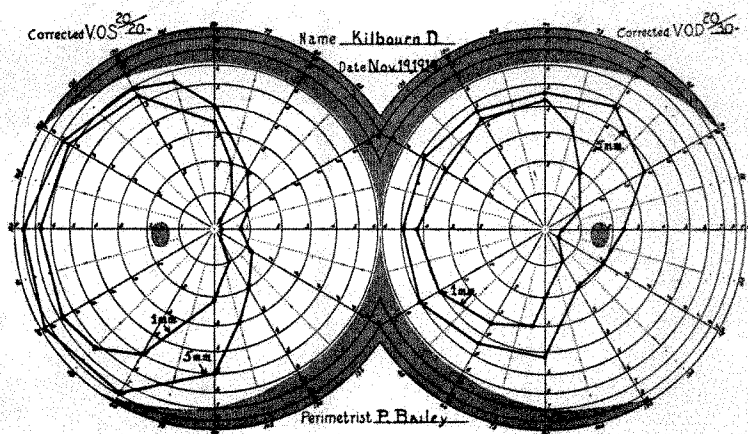


FIG. 13 (*Case 7*).—Pre-operative fields illustrating the crescentic type with tendency to lower quadrant defect on the right side (perimeter only).

A left subtemporal decompression was performed on November 13, 1919, but as there was little improvement a left occipital bone flap was turned down on November 25. At this session a large medulloblastoma was disclosed and removed as radically as possible.

The patient was discharged with good visual acuity on December 7, 1919. He reported again on April 17, 1922, and fields taken at that time still showed sparing of the macula with visual acuity nearly normal (fig. 14).

Two patients only in this group showed bisected macular bundles. One of these had a spongioblastoma polare, and the other an echinococcus cyst. The record of the latter may be given as an example.

Case 8.—M. G., an Italian, aged 41 (surgical number 28014), was referred on January 18, 1927, by Dr. A. De Feo of Chicago, Ill.

His present illness consisted entirely of headaches and failing vision over a period of two years.

Neurological examination showed a little weakness of the left side, bilateral choked discs of $2\frac{1}{2}$ diopters and the left homonymous hemianopsia illustrated in fig. 15.

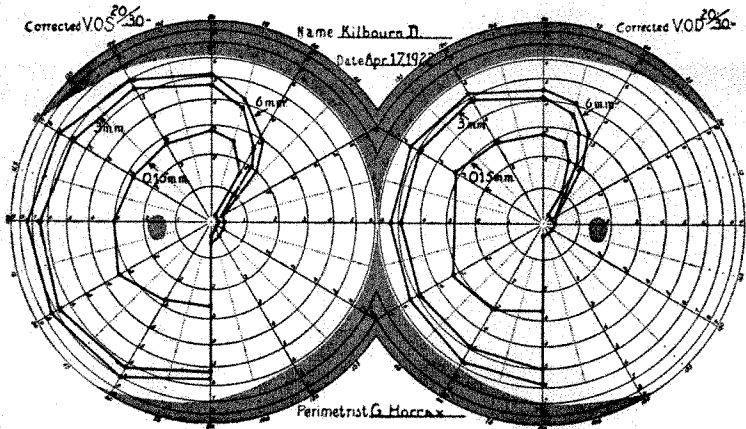


FIG. 14 (*Case 7*).—Fields taken three years after operation showing tendency to homonymous right lower quadrantal defects (perimeter only).

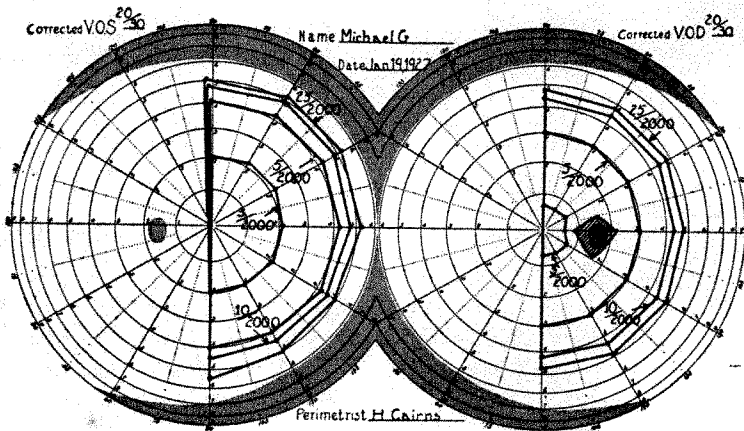


FIG. 15 (*Case 8*).—Pre-operative fields showing hemianopsia with probable bilateral bisection of macula (screen only).

A ventriculogram was performed on January 28, 1927, and this showed the occipital horn of the right ventricle displaced downward and forward. For some reason operation was delayed and the patient lapsed into coma, but was brought back to consciousness by an intravenous injection of hypertonic saline.

On January 30, a right subtemporal decompression was performed, and on February 9 an occipital bone flap was turned down. The lesion was located in the occipital lobe and complete extirpation accomplished.

Convalescence was stormy with some elevation of temperature for two weeks. The bone flap was re-elevated but no clot found. He gradually improved, and at the time of discharge his fields had begun to fill out a little in the lower halves (fig. 16).

Comment.—Only one other example of hydatid of the brain is on record at the Peter Bent Brigham Hospital, but there are three in Wilbrand and Saenger's series and two among the fourteen occipital tumours collected by Duret.

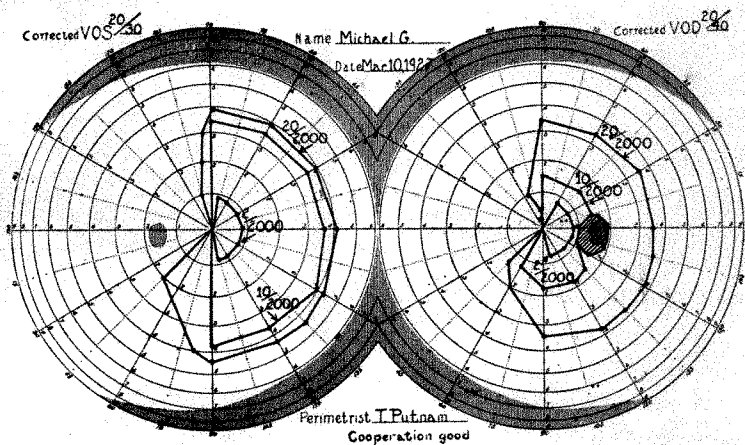


FIG. 16 (Case 8).—Post-operative field illustrating slight tendency to filling out especially in lower quadrants (screen only).

The case, however, is not cited merely because of its rarity, but because it is the single example in our series of purely occipital tumours in which there was a tendency either before or after tumour removal toward an upper homonymous defect rather than a lower. Furthermore, in the post-operative fields there is a distinct tendency toward a horizontal sector defect.

Visual hallucinations.—In a previous communication upon this subject by one of us (Horrax [7]) both the temporal and the occipital lobe tumour cases verified in the clinic to 1923 were investigated as to hallucinatory phenomena. Up to that date there had been no instance of true "formed hallucinations" in occipital growths and these phenomena therefore were reported as significant of involvement of the optic tracts within the temporal lobes, or possibly to an invasion of the optic thalamus.

In the present series of purely occipital tumours six patients (15 per cent.) gave a history of having had visual hallucinations of one sort or another before their tumours were removed. Four of these described the appearances in such a way as to leave no doubt but that they were "unformed" images such as spots, circles or flashes of light, but one of the four, as will be told, saw also vivid "formed" figures after operation. One of these descriptions has been given fully under Case 3 above. Another patient (C. B., surgical No. 19638) said that she had consulted an oculist a year and a half before admission to the hospital because she "had floating spots before her eyes." Occasionally also she "saw a flash of light." These flecks of light were temporary and she did not remember whether they appeared toward one side or the other. Her tumour was a large (188 grm.) meningioma at the occipital pole and she had a left homonymous hemianopsia with sparing of her macula.

A third patient (V. R., surgical No. 35792) had had for twelve years episodes of seeing a sparkling light in front of her eyes. This light "would begin circling around in ever increasing circles" until the bulb or source of light would seem to involve her whole visual field. This gradually enlarging circle would reach its maximum and disappear in about fifteen minutes. Associated with the hallucination she had a feeling of nausea and dizziness. There was no projection of the image to either side, but the vision was followed by a period of hemianopsia which might last one to two hours, and this was succeeded by a headache. She could not tell whether her hemianopsia was always on the same side. Her tumour was a large cyst with a mural nodule lying in the anterior portion of the occipital lobe. She had a complete right homonymous hemianopsia with bisection of the fixation point.

The fourth of these patients who experienced crude hallucinations (W. G., surgical No. 28111) described the episode merely as a "halo of white light" opposite the right edge of his visual field. He had a right homonymous hemianopsia with spared macular fibres. This type of hallucination had occurred before operation, but for four days after the removal of a large, high occipital meningioma he had exceedingly vivid, typical formed hallucinations. The pictures came and went so rapidly that he could scarcely recognize all of them. They were all flat and unreal. Many were coloured. They were spaced about ten minutes apart and he dictated long lists of them to his attendants. They appeared first in the upper quadrant and later skipped about from one part to another, but always on the blind side. Those above the horizontal appeared very large, those below were of natural size. The most vivid

image was one of Dante which resembled the well-known profile with long nose and a wreath on the head. Twice he saw the figure of Theodore Roosevelt, once in a white vest and once in a frock coat. One of the few figures which had any motion was a white Punchinello with a white face who kept bowing from the waist. He also saw strange men walking, dogs, goats, and lions, a Japanese warrior in tortoise-shell armour, a fat man blowing his nose, and a host of unrecognized figures.

The hallucinatory phenomena of the remaining two patients were as follows: In one, Case 6, recorded in the earlier part of the paper, there was seen a vague image of some one standing in the doorway on her right side, this appearance coming after a left subtemporal decompression but before the operation for tumour removal. The other patient (L. S., surgical No. 30335) saw signs hung up in the room although actually no signs were there. He also asked his wife whether or not there were bugs crawling along the wall. He likewise saw colours always to his left side. This patient was in an exceedingly drowsy, almost semi-conscious state, so that fields of vision could not be taken. He gave a history, however, of a left homonymous hemianopsia. His tumour was a glioblastoma of the right occipital pole.

From the foregoing data, therefore, it is still our impression that true formed figure hallucinations are not produced by occipital tumours. The one striking example of such phenomena in our series occurred only after an extensive operation and the images may well have been called forth by trauma and irritation of contiguous areas. Of the remaining two instances, one was exceedingly vague and occurred after a temporal decompression, the other episode was elicited from a semi-conscious individual, the characteristics of whose hallucinations resembled more nearly those of general intracranial pressure or delirium tremens. It is interesting in this connection that Harris [8] in 1897, after an extensive study of clinical material, came to the same conclusion regarding the crude type of visual hallucinations, but was inclined to believe that the complex images, although elaborated perhaps in the angular gyrus, were "due to reflex irritation from a lesion in or near the cuneus, but which may be in the optic radiations or optic tract."

DISCUSSION.

In the present investigation an attempt has been made to set forth certain effects upon the visual apparatus of occipital lobe tumours. All the cases in the series were verified as to their situation and their pathology either by operation or autopsy. Even so, we realized that some of

the tumours may have involved adjacent portions of temporal or parietal lobes, but an effort was made to eliminate these so far as possible by careful reference either to the detailed account of operation, including usually a sketch made at the time, or to the post-mortem specimen or photograph. In confining our study to purely occipital tumours, therefore, both the investigation and its results differ considerably from the studies upon occipital tumours hitherto reported by those who have included tumours involving neighbouring brain areas, in some instances rather extensively.

Several striking features relating to the visual fields are apparent in this series. Perhaps the most important is that in a large proportion of the cases showing contralateral homonymous field defects the central fibres were spared. This was especially manifest in the meningioma group, a fact which we believe to be highly significant since they, of all the growths in this area, were the ones which could be said to be entirely occipital, as a rule occupying the situation of the occipital pole.

Two explanations, at least, may be offered to account for the preservation of central vision in patients with occipital lobe tumours. One of these would be on the basis of a double cortical representation for the macula with the secondary set of fibres decussating in the posterior end of the corpus callosum according to the ideas of Lenz [9], and of Foerster [10]. That the assumption of such an interpretation for preservation of macular vision is open to grave criticism was shown by one of us (Putnam [11]), in a comprehensive review of personal and other investigations bearing upon this point. In the case recorded by Foerster in support of this theory a patient with normal visual fields was explored for a supposed tumour in the region of the corpora quadrigemina. At this operation the posterior end of the corpus callosum was divided and the right occipital pole excised. The patient had a complete left homonymous hemianopsia with bisection of the macular fibres post-operatively, but this does not prove that the result would not have been similar if the occipital pole only had been removed without section of the corpus callosum.

A more plausible explanation, it seems to us, is offered by Allen. He believes that so long as a minimal number of visual fibres remain undestroyed or completely compressed, together with preservation of the cortex of the occipital pole, central vision remains unimpaired. Such a sequence of events is illustrated admirably by meningioma cases in which the whole occipital area, although often markedly compressed, is nevertheless not destroyed, and it is these patients who so frequently

retain central vision in the presence of an otherwise complete homonymous hemianopsia. In one case in the present series, extirpation of a 200-grm. meningioma from the occipital pole led to loss of central vision which had been present before operation, although the corpus callosum was well outside of the operative field. In another instance (Case 5) macular vision returned after extirpation of a tumour situated well posterior.

A second point concerning visual fields relates to the situation of homonymous quadrantic defects. Only five patients showed this type of field, so it is unwise to draw any far-reaching conclusions from this small number. However, in all five instances the quadrant was always the lower one. That upper homonymous quadrant defects may be caused by an occipital tumour is clearly evident in Allen's report (Case 3), but from our experience we should regard them as exceptional. A possible tendency to upper quadrant defect may be seen in the fields of Case 8, but only after operation, and in combination with other peculiarities practically unknown in defects due to temporal lobe lesions.

A third characteristic of the sector defects caused by occipital tumours is that they subtend a variable arc. The sector defects caused by temporal lobe lesions are almost invariably quadrantic; that is, they are bounded by the horizontal as well as the vertical meridian. This is well shown by the case reports in the previous paper of this series [1]. In the present group of cases, the upper border of the defect may lie below the horizontal (figs. 3 and 4), or above it (figs. 5 and 14).

A fourth feature of the field defects in this group is their tendency to be relatively congruous on the two sides respectively. That is, when the field of one eye is superposed on that of the other they correspond closely. Except in the instance of complete hemianopsia the defects due to temporal lobe tumours are usually strikingly dissimilar. In one case reported in the preceding paper [1] there was an almost complete quadrant defect in one eye, and a normal field in the other. The association of a homolateral quadrantanopsia and a contralateral complete hemianopsia is not rare in cases of temporal tumour.

In several cases in this group the defect described by Holmes [12], consisting of a wedge-shaped scotoma extending to the fixation-point on the horizontal meridian, was seen (figs. 13 and 16). This type of defect probably never occurs except with occipital lesions.

The differential diagnosis between temporal and occipital tumours.—This may be difficult or impossible without the aid of ventriculography, but we believe that certain features which have been stressed here will

be helpful. For a comparison of the visual aspects the perimetric charts of 121 cases of verified temporal lobe tumours were examined. Among these, fields were not available in 46. Of the remaining 75, normal fields were revealed in 20, complete hemianopsia with involvement of the macula was shown in 17, upper quadrant defects in 16 and lower quadrant defects in 13. A more or less typical sparing of the macula occurred in 5. Thus it is apparent that normal fields, quadrant defects (especially upper) and hemianopsias with bisection of the fixation point are infinitely more frequent with temporal lobe tumours than with occipital. The preponderance of fields showing spared central fibres in the latter would seem to put the burden of proof upon the person who said that a patient with such fields had not an occipital growth.

CONCLUSIONS.

(1) Intracranial tumours confined to the occipital lobes are comparatively rare, occurring in only forty instances in a series of 1,881 verified intracranial growths.

(2) In an extremely large proportion (73.6 per cent.) of patients having tumours confined to or chiefly compressing the occipital lobe, fields of vision show a contralateral, homonymous hemianopsia in which the central fibres remain unaffected. This is particularly true of meningiomas situated at the posterior end of the occipital lobe.

(3) An upper quadrantal homonymous defect of the visual fields was not disclosed in any case of the series, and we therefore regard its occurrence as rare in strictly occipital tumours.

(4) Visual hallucinations occurred in six patients (15 per cent.) before operation for tumour removal. Careful investigation of these supports the idea that complex "formed" images are not provoked by occipital tumours.

(5) The differential diagnosis between temporal and occipital tumours may be impossible without ventriculography. The high incidence of spared central fibres, together with the rarity of upper quadrantal defects in the latter, are helpful, since bisection of the macula and upper quadrantanopsia are frequent in the former. Other differential features are the relatively greater tendency to the true quadrantic form (bounded by the horizontal meridian) in defects due to temporal lobe lesions, and their greater incongruity as compared to those due to tumours of the occipital lobe.

The authors wish to take this opportunity of expressing their

appreciation to Dr. Harvey Cushing for his kindness in permitting them to report these cases from his clinic.

REFERENCES.

- [1] CUSHING, H. "The Field Defects produced by Temporal Lobe Lesions," *Brain*, 1921, **44**, 341-396.
- [2] *Idem*. "Intracranial Tumours." 1932. C. C. Thomas, Springfield.
- [3] WILBRAND and SAENDER. "Die Neurologie des Auges." Wiesbaden, 1917, **7**.
- [4] ALLEN, I. M. "A Clinical Study of Tumours involving the Occipital Lobe," *Brain*, 1930, **53**, 194-243.
- [5] DURET, H. "Les Tumeurs de l'Encéphale." Paris, 1905.
- [6] FRAZIER, C. H., and WAGGONER, R. W. "Tumours of the Occipital Lobe: A Review of Forty Cases," *Arch. Neurol. and Psychiatr.*, 1929, **22**, 1096-1099.
- [7] HORRAX, G. "Visual Hallucinations as a Cerebral Localizing Phenomenon," *ibid.*, 1923, **10**, 532-545.
- [8] HARRIS, W. "Hemianopsia, with Especial Reference to its Transient Varieties," *Brain*, 1897, **20**, 308-364.
- [9] LENZ, G. "Zur Pathologie der zerebralen Sehbahn unter besonderer Berücksichtigung ihrer Ergebnisse für die Anatomie und Physiologie," *Arch. f. Ophth.*, 1909, **72**, 1-85, 197-293.
- [10] FOERSTER, O. "Beiträge zur Pathophysiologie der Sehbahn und der Sehsphäre," *Journ. f. Psychol. u. Neurol.*, 1929, **39**, 463-485.
- [11] PUTNAM, T. J. "Studies on the Central Visual Connections. III," *Arch. Neurol. and Psychiatr.*, 1926, **16**, 566-596.
- [12] HOLMES, G. "A Contribution to the Cortical Representation of Vision," *Brain*, 1931, **54**, 470-479.

A NOTE CONCERNING THE RELATION OF THE FRONTAL LOBES TO POSTURE AND FORCED GRASPING IN MONKEYS.

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ACCORDING to anatomical definition, the frontal lobe is that part of the neopallium lying anterior to the central sulcus (Gray [7]), but in considering the functional activities of this area of the brain three important regions can be recognized. In fact, from the point of view of functional analysis it seems desirable to disregard the anatomical definition altogether, and to reserve the adjective "frontal" for the third of the following functional areas. We are aware that this subdivision of the frontal lobe is not new (see Hines [8]), but it has seemed to us that further experimental support for it would be welcome.

(1) *Motor area*.—This lies on the surface of the anterior central gyrus; it is bounded posteriorly by the central sulcus, and anteriorly by the lower limb of the inferior precentral (arcuate) sulcus and an ill-defined superior limit generally associated in lower primates with the superior precentral sulcus.

(2) *Premotor area* ("Area 6" of Brodmann [2, 3]).—This, in primates below man, is bounded anteriorly by the superior limb of the inferior precentral sulcus (arcuate 1) and its arbitrary continuation to the midline (see below). Its posterior boundary is variable but corresponds roughly with the superior precentral sulcus, and can only be ascertained by faradic stimulation. In monkeys the superior and inferior precentral sulci do not reach the midline of the hemisphere, but there is anatomical and physiological justification for extending the boundaries to the midline, as indicated in fig. 1, since the area so circumscribed corresponds with the special agranular architectonic "Area 6" of Brodmann.

(3) *Frontal area*.—By the frontal area we refer to the region of the neopallium anterior to the inferior precentral sulcus and its arbitrary extension to the midline. By some authors, e.g., Hines [8], this is referred to as the "prefrontal area". We are not yet prepared to

define the exact medial and inferior limits of the frontal area, but for the present we have taken as the ventral boundary the tissue lying anterior and medial to the external orbital sulcus. Our reasons for not including the so-called premotor area with the frontal area will be evident from a perusal of this paper.

We have attempted to make the preceding definitions conform to the B.N.A. terminology, and we believe that they are applicable to all primate forms, provided the well-known arcuate sulcus of the monkey has its homologue in the inferior precentral sulcus of man and the higher apes.

We propose first to describe the characteristic syndrome produced by bilateral extirpation of the frontal areas of monkeys, i.e., the entire region anterior to the arcuate sulci.

BILATERAL REMOVAL OF FRONTAL AREAS.

Extirpation of the "prefrontal" region in dogs and cats is said to cause a permanent alteration of posture in the extremities opposite to the lesion. Indeed Olmsted and Warner [14] believed that they could induce a state akin to decerebrate rigidity by making a bilateral frontal lesion in the cat. The general result was confirmed by Langworthy [11], who pointed out that the hypertonia disappears if the *entire* motor area is also removed. Doubt has been expressed, however, concerning the inference that the lesions in these experiments were restricted to the prefrontal area. The premotor and motor areas, as is well known, lie only a few millimetres posterior to the frontal area in cats, and any lesion of this region is likely to impinge upon the premotor and motor cortex. It has therefore seemed worth while to record a series of observations made for another purpose in monkeys, since in the monkey the frontal area is more considerably developed and can be precisely delimited from the motor area.

Our preliminary observations were made upon two monkeys (*Pithecus rhesus*), highly trained in problem-box manoeuvres (see [9]), from which the frontal areas were removed from both sides simultaneously under sodium-amytal anaesthesia. The extirpations were made with a Bovie electrosurgical unit which allows precise anatomical delimitation of the lesion. The exact extent of the ablation in the second animal is indicated in fig. 1. Each area was taken out as a single block of tissue and the extent of the lesion could be ascertained from examination of the block of tissue removed. Full details concerning the surgical procedure and the effects of the lesion upon

acquired skilled habits, learning, etc., will be recorded at a later date.

For our present purpose we have only to report that complete bilateral destruction of the frontal areas has, in our experience, produced no permanent alteration of posture and no motor deficit in the extremities. After the procedures the monkeys were perfectly coordinated but they exhibited a striking condition characterized by a very great increase in spontaneous motor activity with constant restlessness, a syndrome which one of us has previously described [9, 10], following

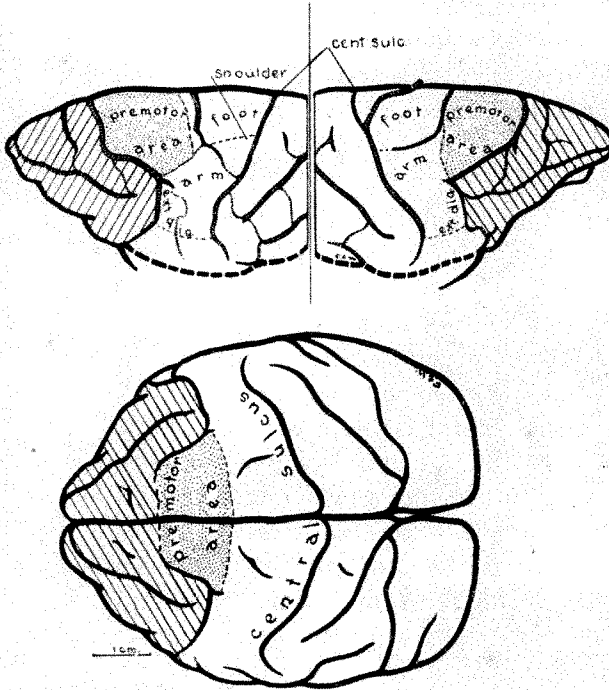


FIG. 1.—Composite representation of the two hemispheres of a rhesus monkey, exposed simultaneously at operation, May 19, 1932. Above are portions of the lateral surfaces of the hemispheres drawn accurately to scale from direct cellophane tracings made at operation. Below, a reconstruction of the hemispheres viewed from above. The premotor area, which was not removed, is stippled; the cross-hatched frontal areas were ablated simultaneously. In all subsequent figures, which are also three-quarters life size, stippling denotes the premotor area and cross-hatching the lesion.

destruction of the frontal areas in monkeys. With the augmentation of motor activity there is an associated increase in appetite, which sometimes involves ingestion of two to three times the normal amount of food, and despite this circumstance the animals generally lose weight.

At no time was there evidence of forced grasping in animals in which the lesions were restricted to the frontal area.

BILATERAL REMOVAL OF FRONTAL AND PREMOTOR AREAS.

If one includes the premotor area in the extirpation of the anterior part of the hemisphere, the symptoms resulting are quite different from those just described. In two monkeys, one *Pithecus rhesus*, and the other *P. cupidus*, we have carried out sharply circumscribed bilateral extirpations of all cortical tissue anterior to the excitable area. In both experiments we were careful to undercut the cortex somewhat anteriorly so as to avoid injury to the underlying basal ganglia.

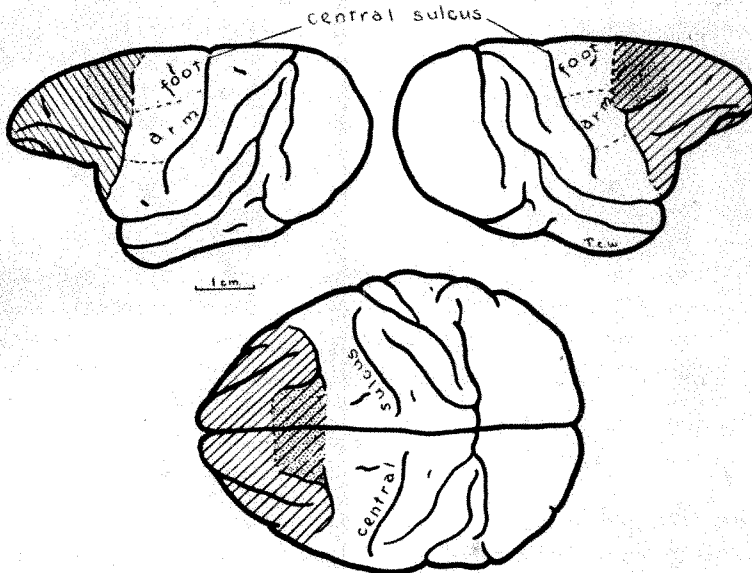


FIG. 2 (*Experiment 1*).—Above, the lateral surfaces of the two hemispheres reconstructed from cellophane tracings made at operation; the frontal and premotor areas were simultaneously removed from both sides. Below, the two hemispheres viewed from above (reconstructed). The area lying between the central sulcus and the premotor area represents the excitable motor cortex.

Within one to two days of operation both the animals began to show strongly marked forced grasping, especially of the upper extremities (but also present in the lower), perseveration, slowness of movement, and particularly striking retardation in the initiation of movement, e.g., grasping for food. There was no hypertonia or true spasticity. The mental state of the animals appears to be one of rather marked torpor, and the sluggish motor behaviour is in striking contrast to the incessant activity of the "frontal" animal.

The area removed from the second of the animals just mentioned is indicated in fig. 2. Details of the observations on this monkey are given in the following protocol.

Experiment 1.—Mature male Java monkey (*Pithecus cupidus*), weight 5,250 gm. Bilateral bone-flap with extirpation of all cerebral tissue anterior to motor area on both sides. Forced grasping; perseveration; retardation of movement; mental torpor; motor power essentially unchanged. [Frontal IV.]

The subject of the experiment was a large, fully matured Java monkey, which had been under observation in the laboratory for a period of nine months prior to operation. He was a strong, aggressive animal, given to mimicry and certain characteristic and rather outlandish gestures frequently executed in order to attract attention.

Operation (July 5, 1932).—Under sodium-amytal anaesthesia (2.6 c.c., 10 per cent. intraperitoneally) virtually the entire surface of both cerebral hemispheres was exposed by reflection of bone-flaps bilaterally. This made it possible to trace the chief anatomical landmarks of both cerebral hemispheres on cellophane, and to determine the limits of both excitable motor areas. The diagram indicated in fig. 2 is reconstructed from the cellophane tracings of the cortex and indicates the distribution of excitable points on the motor area as well as the regions which were extirpated. It is significant that strongly developed extensor responses were obtained along the arcuate sulci on both sides, up to the point where it bends forward. The foot representation was somewhat less definite anteriorly, and the lesion ultimately made had its posterior boundary about 1 mm. anterior to the excitable area for the lower extremity.

The lesion was carried out with the new model Davis-Bovie electrosurgical unit described elsewhere [5]. The large veins passing into the sinus were first carefully coagulated and the cortex then incised with the cutting current to a depth of about 4 mm. along the line of intended extirpation. The deeper structures were cut through with a spatula and the entire block of tissue removed from each side in one piece. The spatula was directed somewhat anteriorly in order to avoid the anterior end of the basal ganglia. Subsequent examination of both blocks of tissue failed to reveal any trace of the basal ganglia. Examination of the tissue removed also revealed that the ventral limits of the extirpation corresponded approximately with the external orbital sulcus. The right side, however, included slightly more tissue than the left.

The bone-flaps were replaced and were accurately approximated by resuturing the temporal muscle with interrupted silk.

Post-operative notes.—The animal made a prompt recovery from anaesthesia. During the first two or three days it was rather dazed, but executed purposeful movements and made movements toward food when it was brought into its range of vision. During these first few days it would stand for hours at a time with head slightly depressed, gazing vacantly into space.

Forced grasping.—During the first day this was poorly developed and was somewhat more marked on the left than right. On the second day the animal would support its weight for one to two minutes with either hand, and appeared to exhibit a fairly typical forced grasping response. This continued throughout the first week of observation without essential change. Light

stroking of the palmar surface and bases of fingers served to evoke a vigorous grasp, from which the animal would not ordinarily relax until both feet were securely on the ground and the arms brought to the level of the umbilicus. Frequently, also, vigorous grasping was seen in the foot, and on one occasion was sufficient to support its weight over a period of several minutes. The involuntary character of the grasping reflex of the foot was, however, less definite than in the hand. After the end of the first week the animal commenced to feed itself voluntarily with its hands, and though it often appeared to have difficulty in relaxing its grasp on food, the grasp reflex diminished in intensity, particularly at feeding times. The reflex was at its height on the sixth day after operation and was still sufficient to maintain its weight after more than two weeks.

Groping.—After the first week, when any object was brought within a radius of 1 to 2 ft. in its field of vision the animal would grasp it slowly but firmly after a latency of ten to thirty seconds; once grasped the object would be held for minutes at a time without change of attitude. Sometimes when the object was held just out of its reach the animal would direct its hand toward it and the posture so induced would be retained, as if "frozen" in position for minutes at a time.

Perseveration.—All purposeful movements were notably slow in starting during the first three weeks and always continued after their usefulness was over. Thus, when the hand was brought to the face with food it stayed there and often clutched the food while the animal was at the same time trying to consume it. Once a movement, such as walking or chewing, was initiated, the animal would continue the movement for an unlimited time, to the exclusion of all other activity and in complete disregard of external stimuli which would readily divert a normal monkey.

Posture.—There was no hypertonia and no true spasticity in any of the extremities following operation. The attitude of the animal, however, was somewhat unusual, in that he tended, especially during the first week, to stand for long periods of time with his head depressed. The postural disturbances were chiefly those associated with its forced grasping and groping.

Subsequent history.—The animal was kept in the laboratory for ninety-seven days before a second operation was performed. During this time speed of reaction gradually increased until motor performance appeared normal. During the third and fourth weeks, forced grasping and groping were the most prominent features in the animal's behaviour. It was usually found hanging from the bars of the cage. After the fifth week these symptoms slowly subsided, and it became more and more difficult to elicit reflex flexion by stroking the palms. During the fifth week, voluntary grasping reappeared for the first time, and increased in strength. By the time of the second operation the only sign of forced grasping was a tendency to grasp any object placed within its field of vision. All grasps could be relaxed voluntarily.

At a second operation on October 10, 1932, the left motor area was removed. Motor power returned sufficiently during the first day so that both right limbs

were used in walking, but were dragged in a circling movement. After this, although strength increased somewhat, there was very little improvement. The right limbs continued to be dragged, and finely co-ordinated movements could never be executed. At rest, the right limbs were as flaccid as the left; when struggling, there was noticeable hyperextension of the right extremities. At no time was the animal able to pick up objects with the right hand. Involuntary grasping, however, reappeared in this hand on the second day, became very marked on the fourth day, and persisted until the third operation on the thirty-first day, although after the first week it was less easily elicited.

A *third operation* was performed on November 17, 1932, in which the right motor cortex was removed. Immediately on coming out of anaesthesia, very marked bilateral forced grasping and paroxysmal groping appeared in response to any type of stimulus. When left undisturbed, the animal lay with hyperextended extremities usually grasping objects tightly with both hands. There was marked resistance to passive manipulation which was greater on the left than on the right.

This picture persisted until the animal was sacrificed on the sixth day (following twenty-four hours of prostration and vomiting). Autopsy showed intussusception as the cause of these terminal symptoms. All cortical tissue anterior to the central sulci on both sides had been destroyed. The basal ganglia and the thalami presented no sign of injury.

It is thus evident that when the premotor area is included in the frontal lesion the resulting picture differs strikingly from that produced by a pure frontal lesion. The most noteworthy additional feature is the forced grasping and groping, and we believe this to be a sign of a much more profound underlying disturbance, involving difficulty in the initiation and slowness of all voluntary movements, perseveration, and diminished ability to execute highly skilled movements. The incessant activity and restlessness of a pure frontal lesion was also notably lacking in the animal just described, as in Jacobsen's [9] animal T, in which the lesion also involved the premotor area.

The observations on forced grasping are in keeping with Richter and Hines' [15] recent announcement that extirpation of Brodmann's "Area 6" of itself causes involuntary forced grasping.

ISOLATED REMOVAL OF THE PREMOTOR AREA (IN PART AND COMPLETELY).

Richter and Hines [15] report that extirpation of the premotor area from one side causes a transient grasp reflex, which becomes greatly accentuated on both sides when the area is removed bilaterally.¹ Our first observations were carried out on a green monkey (*Lasiopyga*

¹ In Richter and Hines' preliminary note [15] announcing their discovery that forced grasping can be induced experimentally by destruction of the premotor area, they state: "It

callitrichus, fig. 3a) and a baboon (*Papio gelada*, fig. 3b), from which only the superior part of the premotor area, i.e., only the part opposite the foot representation, was destroyed (fig. 3). In these two animals forced grasping was not observed in either the foot or the hand at any period following the operation. It would thus appear that extirpation of the superior part of the premotor area does not cause forced grasping.

Further observations were made on a green monkey and a baboon, from each of which the whole of the premotor area (fig. 4) as defined by Brodmann was destroyed. The result in the case of the green monkey is indicated in the following protocol.

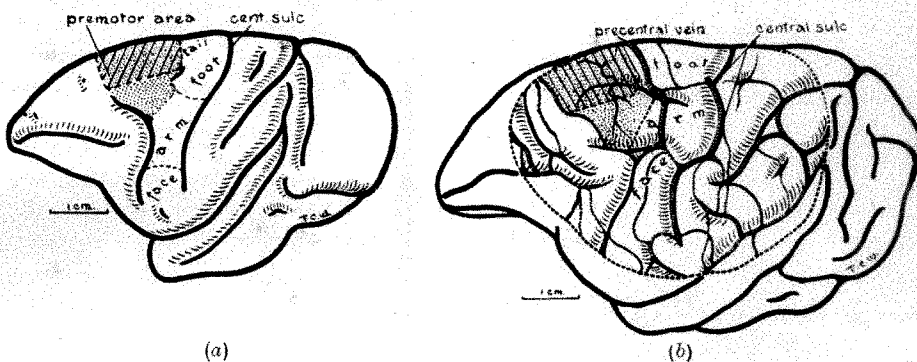


FIG. 3.—(a) The cerebral hemisphere of a green monkey (*Lasiopyga callitrichus*) as exposed at operation, showing the premotor area of which the superior portion (cross-hatched) was removed. This animal did not exhibit forced grasping. (b) A portion of the left hemisphere of a baboon (*Papio gelada*) as exposed at operation, of which the superior part (cross-hatched) was removed. This animal similarly failed to show forced grasping. The remaining part of the hemisphere was reconstructed from a preserved brain of the same species.

Experiment 2.—Mature female green monkey (*Lasiopyga callitrichus*), weight 2,500 gm. Left-sided bone-flap with sharply circumscribed extirpation of entire premotor area. Motor area intact and responsive following extirpation. Immediate involuntary forced grasping of right upper extremity with slight motor deficit and obvious impairment of skilled movements. [Premotor V].

A well-developed specimen of the common green monkey (*Lasiopyga callitrichus*) was used, which had been under observation in the laboratory for several weeks. It was well coordinated and aggressive but readily handled.

was found that the reflex can be elicited consistently only by removal of the premotor area, area 6 of Brodmann, the medial as well as the lateral surfaces, down to the level of the corpus callosum." It is clear that they should receive sole credit, not only for having first experimentally established the fact that lesions of the premotor area give rise to forced grasping, but also for having proved, as is implied in the sentence just quoted from the abstract of their communication made at Philadelphia, April 28, 1932, that lesions elsewhere in the frontal lobe fail to give this symptom. Drs. Richter and Hines propose to publish full details concerning their studies in the near future.

Operation (July 18, 1932).—Under sodium-amytal anaesthesia (1.2 c.c. intraperitoneally) the entire left cerebral hemisphere was uncovered by reflecting a large five-sided bone-flap, the superior limits of which extended to the right of the midline. The chief markings were traced upon cellophane (fig. 4), and a careful map was made of the excitable points on the motor area. As the animal was lightly anaesthetized the anterior limit of the foot and arm areas could be accurately determined and this was taken as the posterior boundary of the premotor area. Along the lower limit of the arcuate sulcus well-marked extensor movements of the right wrist and fingers were obtained. Along the central sulcus itself characteristic motor responses were obtained of the various muscle-groups on the right side of the body.

Extirpation of the premotor area was carried out with the new model Davis-Bovie unit. The posterior margin coincided exactly with the anterior limit of the arcuate sulcus and its arbitrary extension to the midline. The cortex was incised to a depth of about 5 mm., the edges being made perpendicular, and the block of tissue was removed in one piece. The lesion, which extended down the medial surface of the hemisphere 7 mm., is depicted in fig. 4. Extension of the fingers was obtained from the anterior margin.

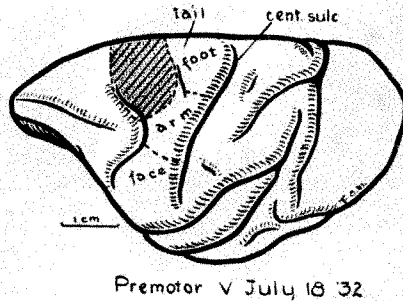


FIG. 4 (*Experiment 2*).—The left hemisphere of a green monkey (*Lasiopyga callitrichus*) reconstructed from cellophane tracing made at operation, showing the premotor area, which was entirely removed. This animal showed forced grasping immediately after operation.

There had been no bleeding during the extirpation and the crater of the lesion was left quite dry, and the dura drawn down again over the entire cortex before closure.

Post-operative notes—forced grasping.—The operation was completed at 12.30 p.m., and the animal had begun to recover from its anaesthesia two hours later, at which time there was definite involuntary grasping of the right upper extremity. At 4.30, i.e., four hours after operation, the grasping was well developed and was evoked by lightly stroking the distal surface of the palm. The next day the slightest stimulus applied to the palm evoked the response and with it a fairly vigorous flexor contraction which, with the flexor response of the digits, was sufficient to support the animal's weight indefinitely. The response was always augmented when the animal became

excited and during periods of excitement it seemed quite unable to release its grasp. On the third day forced grasping was even more readily evoked than on the second.

Motor deficit.—There was obvious awkwardness in the use of the right upper extremity immediately after operation. It could be used for climbing and running, but finely skilled movements, e.g., feeding or picking up small objects, were done entirely with the left hand. At rest the extremity assumed a semiflexed hemiplegic posture.

Subsequent course.—Forced grasping and awkwardness of the extremities continued in marked form throughout the post-operative period. The animal was sacrificed for Marchi studies on the eighteenth day. A report concerning anatomical findings will be published subsequently in our more detailed account of the functions of the frontal lobes in primates.

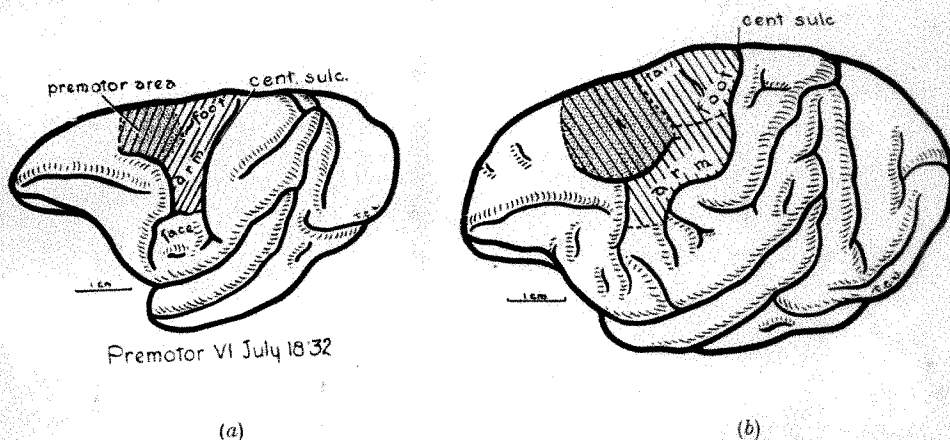


FIG. 5.—(a) The left hemisphere of a green monkey (*Lasiopyga callitrichus*) reconstructed from cellophane tracing made at operation. The entire motor and premotor areas were removed. This animal showed marked hemiplegia and after three days forced grasping. (b) The left hemisphere of a baboon (*Papio gelada*) reconstructed from a cellophane tracing made at operation. The entire motor and premotor area was removed. This animal showed symptoms of marked hemiplegia and after five days forced grasping.

REMOVAL OF THE MOTOR AND PREMOTOR AREAS SIMULTANEOUSLY.

In our laboratory we have records of an extensive series of observations on the results of lesions restricted to the excitable motor area in monkeys, baboons, gibbons, an orang, and many chimpanzees, and in none of them was forced grasping observed, except in a gibbon in which the premotor area was inadvertently encroached upon in the course of an extensive extirpation of the arm area. It is therefore important to know whether a lesion embracing *both* the excitable and the premotor areas would cause such a response. Our interest in this problem arose in the first instance in the attempt to ascertain why cortical lesions produced

a flaccid monoplegia while capsular lesions give rise to spasticity, rather than as an investigation of forced grasping.

We have found that lesions extending from the central sulcus to the posterior margins of the frontal areas defined above (see fig. 5 *a* and *b*) also cause hemiplegia both in monkeys and baboons (*Pithecus rhesus*, *Lasiopyga callitrichus*, *Papio gelada*) which is less flaccid in character than that occurring after lesions restricted to the motor area. In addition, forced grasping appears in the monkey after a latency of several days. In the baboon forced grasping appeared five to six days after removal of the motor and premotor areas (fig. 5*b*) but in less marked form than in the monkey. We have not yet investigated the phenomenon in the gibbon or chimpanzee. Forced grasping is said to cease in man when the true motor area becomes extensively involved, but we are not yet in a position to account for the difference between man and monkey. It may be recalled, however, that a Babinski response does not occur in monkeys after a lesion of the motor foot area [5].

DISCUSSION.

It seems obvious, as the Vogts [17, 18] have pointed out, that the distinction between the motor and premotor areas is to be correlated with the disappearance, approximately at the level of the superior precentral sulcus, of the large Betz cells which give rise to the large fibres of the pyramidal system. In the agranular premotor area, the large Betz cells are absent, as is excitability for ordinary strengths of stimulation. The degenerations from lesions of the premotor area do not appear to have been exhaustively studied (see Hines [8]) and it is our intention to make this the subject of a report in the near future; with a few exceptions all of our experimental material is studied by the Marchi method three weeks after operation.

The fact that complete extirpation of the frontal area leads to no disturbance of posture is in harmony with similarly well-controlled observations on human beings, in which extensive resection of the frontal lobe for malignant tumour has failed to cause any postural disturbance or motor disability [12]. This definitely precludes, in our opinion, the belief that the frontal areas participate in or are essential for postural adjustments. The disturbances following lesions of the premotor area are of a different character, and obviously affect the postural mechanism, but they do not lead to pronounced hypertonia. The so-called postural disturbances associated with frontal lesions in man are undoubtedly caused by involvement of the premotor area (see [1]).

In conclusion, our observations and those of Richter and Hines [15] are entirely in harmony with Adie and Critchley's [1] inferences concerning the localizing value of forced grasping *when it occurs precociously and unilaterally*. With Bucy's [4] opinion as to the questionable localizing value of bilateral forced grasping we concur.

SUMMARY.

Analysis of the localization of function in the cerebral hemispheres of primates allows subdivision of the anatomical frontal lobe, i.e., the area anterior to the central sulcus, into three parts: (1) the true frontal area; (2) the premotor area; and (3) the motor area. The anatomical boundaries are defined above. The present communication describes briefly the effects on posture and on the production of the phenomenon of forced grasping, of sharply circumscribed anatomical lesions of these three areas separately and in various combinations (monkeys and baboons). Our conclusions are as follows:—

(1) Simultaneous bilateral destruction of the true frontal area in the monkey has no effect on posture, i.e., does not give rise to hypertonia, and does not cause forced grasping or retardation in motor adjustments ("perseveration"). It does cause a characteristic syndrome, however, marked by greatly increased spontaneous motor activity with an associated augmentation of appetite.

(2) Simultaneous bilateral extirpation of both frontal areas together with the premotor areas causes forced grasping, perseveration, slowness in initiating responses, but no hypertonia, and the postural disturbances which result are primarily those associated with the phenomena of perseveration and forced grasping and groping.

(3) Lesions restricted to the excitable motor area cause flaccid paresis without forced grasping in all primates above the lemurs.

(4) Simultaneous extirpation of the motor and premotor areas causes a less flaccid paresis with the appearance, after an interval, of forced grasping (monkeys).

(5) Richter and Hines have shown that isolated destruction of the whole premotor area on one side causes forced grasping on the opposite side in *Pithecus (macacus) rhesus*. This observation has been confirmed by us in another species of monkey, *Lasiopyga callitrichus*.

REFERENCES.

- [1] ADIE, W. J. and CRITCHLEY, MACD. "Forced Grasping and Groping," *Brain*, 1927, **50**, 142-170.
- [2] BRODMANN, K. "Beitrage zur histologischen Lokalisation der Grosshirnrinde, VII. Die cytoarchitektonische Cortexgliederung der Halbaffen (Lemuriden)," *Journ. f. Psychol. u. Neurol.*, 1908, **10**, 287-334.

- [3] BRODMANN, K. "Vergleichende Localisationlehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues." Leipzig: Barth, 1909, **10**, 324.
- [4] BUOY, P. C. "Reflex-grasping Associated with Tumours not Involving the Frontal Lobes," *Brain*, 1931, **54**, 480-491.
- [5] FULTON, J. F., and KELLER, A. D. "The Sign of Babinski: A Study of the Evolution of Cortical Dominance in Primates." Springfield, Ill.: Thomas. London: Baillière, 1932.
- [6] GEIST, S. D. "The Brain of the Rhesus Monkey," *Journ. Compt. Neurol.*, 1930, **50**, 339-375.
- [7] GRAY, H. "Anatomy of the Human Body." Twenty-first Edition. Edited by Warren H. Lewis. Philadelphia and New York: Lea and Fibiger, 1924, 1418.
- [8] HINES, M. "On Cerebral Localisation," *Physiol. Rev.*, 1929, **9**, 462-574.
- [9] JACOBSEN, O. F. "A Study of Cerebral Function in Learning: The Frontal Lobes," *Journ. Compt. Neurol.*, 1931, **52**, 271-340.
- [10] *Idem.* "Recent Experiments on the Function of the Frontal Lobes," *Psychol. Bull.*, 1928, **25**, 1-11.
- [11] LANGWORTHY, O. R. "The Area Frontalis of the Cerebral Cortex of the Cat, its Minute Structure and Physiological Evidence of its Control of the Postural Reflex," *Bull. Johns Hopkins Hosp.*, 1928, **42**, 20-66.
- [12] LANGWORTHY, O. R. "The Control of Tonus After Injuries to the Brain or Spinal Cord of Man," *Medicine*, 1932, **11**, 225-262.
- [13] NAÑAGAS, J. C. "Anatomical Studies on the Motor Cortex of *Macacus rhesus*," *Journ. Compt. Neurol.*, 1922, **35**, 67-96.
- [14] OLMSTED, J. M. D. and WARNER, W. P. "Latent Periods in the Reciprocal Action of Antagonistic Muscles," *Amer. Journ. Physiol.*, 1922, **61**, 106-116.
- [15] RICHTER, C. P. and HINES, M. "Experimental Production of the Grasp Reflex in Adult Monkeys by Lesions of the Frontal Lobes," *Ibid.*, 1932, **101**, 87-88.
- [16] TILNEY, F., and RILEY, H. A. "The Form and Function of the Central Nervous System." New York: Hoeber, 1923, xxvi + 1020.
- [17] VOGT, GÉOILE, and VOGT, O. "Zur Kenntnis der elektrisch erregbaren Hirnrindengebiete bei den Säugetieren," *Journ. f. Psychol. u. Neurol.*, 1907, **8**, 277-456, 9 pl.
- [18] *Idem.* "Allgemeinere Ergebnisse unserer Hirnforschung," *Ibid.*, 1919, **25**, 275-462, 5 pl.

SYPHILIS OF THE NERVOUS SYSTEM IN THE SUDANESE.

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It is well known that there are some striking differences between the manifestations of syphilis in certain natives of tropical countries and those seen in Western Europeans; outstanding among these are the presence of florid skin lesions and the rarity of general paralysis and tabes dorsalis. Many theories have been advanced to account for these differences, and prolonged controversy surrounds each of them; as instances one may mention the question of dermatropic and neurotropic viruses, the presence of endemic malaria, the absence of civilization and its accompanying mental strain, the length of time since the introduction of the disease in the community, and differences in treatment.

In the literature on the incidence of neuro-syphilis in the tropics there is lamentably little on which one can rely; local conditions are such that complete investigations can seldom be carried out, and diagnoses are frequently made on insufficient evidence. Lacapère [1] has recorded 5,000 syphilitics in Morocco in whom he only saw a few cases of meningitis, five cranial nerve palsies, and twenty-two cases of paraplegia; he also quotes Decrop as seeing only two cases of general paralysis and two of tabes in 84,000 syphilitics examined between the years 1925 and 1930. Raynaud and others [2] examined the cerebrospinal fluids of 324 natives of Algiers, but as they considered either a raised pressure or cells over 1·3 per cubic millimetre as indications of abnormality, their figures cannot be accepted. Webb and Holliday [3] made a survey of nearly 8,000 Bantus of the Buganda tribe, all suffering from syphilis in different stages, and among these they found eighty-three with clinical signs of neuro-syphilis, including cranial nerve palsies, paraplegia, neuritis, myelitis, optic neuritis and atrophy, Charcot's joints, paresis (by which they do not appear to mean general paralysis) and one case that was suspected of tabes.

An interesting form of syphilis occurring in the Bedouin Arabs of the Syrian desert has been described by Hudson [4], who noted the absence of general paresis or tabes; the condition is characterized by its occurrence in childhood without any noticeable primary lesion, its acute course, and apparent absence of any late manifestations other than cutaneous or mucous ulcerations and gummatous bone lesions; it seems that the acute stage may be regarded almost as one of the exanthemata of childhood. A very similar form of the disease exists in parts of Abyssinia [5], where it is estimated that 40 per cent. of the population are infected, and there is even a custom whereby infants are purposely exposed to infection, presumably that they may acquire immunity and be more suitable for marriage at a later age.

Apart from general clinical observations, there do not appear to be any reliable figures to show the frequency of invasion of the nervous system, as gauged by a routine neurological and cerebrospinal fluid examination, in natives of the tropics. In view of this it was thought worth while to study a series of 400 syphilitic Sudanese.

Material.—The 400 cases in this survey were natives of the Sudan (excluding Egyptians or those with any admixture of foreign blood) suffering from syphilis in any stage of the disease. As far as possible they were examined before treatment had been instituted, but as the amount of treatment they received was never more than a few injections of N.A.B. at irregular intervals, the whole series might be considered untreated; in point of fact 186 had treatment at some time, but in most cases it consisted of one injection of N.A.B. at the onset, and possibly a few doses of mercury, after which the patient considered himself cured and did not return to hospital. The average number of injections of N.A.B. was about two per patient.

An effort was made to get a truly representative series, without predilection for those with nervous diseases. The cases included most of the syphilitics attending the Khartoum Civil Hospital between August, 1931, and March, 1932, a number of native soldiers in the Sudan Defence Force and prisoners in the Khartoum prison whose blood was found on routine examination to be Kahn-positive, and syphilitics visited in other parts of the Sudan, including a group in the far South where syphilis had been only recently introduced.

In addition, all the lunatics in Khartoum were investigated, even though their blood-sera were Kahn-negative; they comprised some thirty individuals suffering from dementia, religious mania, and various forms of confusional insanity, but in no single instance was there any

suggestion that syphilis was the causative agent. Only such lunatics as were definitely a danger to themselves or to others were kept under control in the Sudan, but one would expect such a group to include some with general paralysis if it were prevalent.

There is a great preponderance of male patients in this series (83 per cent.) ; it is always more difficult to persuade the women to attend hospital.

The population of the Northern Sudan is very mixed, so that the present survey includes Arabs, Nilotic tribes, negroes and many whose ancestry embraces all of these tribes.

The climate in the north is very hot and dry but, as the population is largely concentrated along the banks of the Nile, malaria is very common ; in fact a recent estimate of the splenic index in some of the villages north of Khartoum showed a figure of over 60 per cent.

Alcohol is not generally used by the natives, but in Khartoum and Omdurman there is a certain amount of drinking ; the favourite spirit is one distilled locally.

The incidence of syphilis in the Sudan may be judged from the fact that the blood of 420 prisoners, apparently in good health, showed in 31 per cent. a positive Kahn reaction.

Florid secondary lesions of the skin and mucous membranes are almost the rule in untreated cases, and soon merge into the tertiary forms, so that it is often difficult to distinguish between a fresh infection and one of many years' standing. Those who receive the usual one or two injections of N.A.B. at an early stage very frequently suffer from most severe recurrences a few months later, and Herxheimer reactions are quite common in the course of treatment. Pains in bones and periostitis are amongst the commonest tertiary manifestations, after muco-cutaneous lesions, but cardio-vascular syphilis (aneurysms and the like) is not uncommon. Congenital syphilis is surprisingly rare ; one sees young infants covered with sores, which readily clear upon treatment, but the congenital disease, in the forms that one recognizes in Europe, is conspicuously absent ; after the early cutaneous lesions there seems to be a latent period of some years, and after this gummata or such tertiary manifestations as periostitis or ulcerations of the palate may appear. This mild and delayed development of the congenitally acquired disease has been remarked by Nögelsbach [5] in Abyssinia, by Hermans [6] in the Dutch East Indies, and by Ferruccio [7] in Somalia.

Method of clinical examination.—In each case the name, age, sex and tribe of the patient was noted, together with details of the history

of the disease, its present manifestations and the treatment received. Where a chancre was present diagnosis was confirmed by dark-ground examination for spirochætes, and in every case the Kahn test was done on the blood-serum. Details were also noted of the history of malaria, in case this should be found to have any bearing on the neurological findings.

A routine investigation of the cranial nerves, including ophthalmoscopic examination of the fundi, was made, and the power and co-ordination of the limbs, the tendon reflexes and abdominal cutaneous responses were noted.

In passing, it is interesting to remark that the patellar tendon-jerk is very difficult to elicit in these people after childhood; this is so constant that one has to consider a response that would in England be taken for normal as distinctly exaggerated. (I attribute it to the habit of squatting and its attendant stretching of the anterior crural group of muscles.) Further, as a result of walking bare-foot, the plantar response can seldom be obtained. Examination of the sensory system was made only when there was any reason to suspect a lesion. In every case where any abnormality was discovered a complete examination of sensation was carried out.

Method of examination of the cerebrospinal fluid.—Lumbar puncture was always performed with a fine needle, the patient lying on his side with the head on the same level as the spine. In each case, except in infants where the result would be valueless, the tension of the fluid was estimated with a manometer, great care being taken to ensure that the patient was not straining; the method employed has been described fully elsewhere [8]; pressures over 20 cm. of fluid were considered abnormal. Within a few hours of obtaining the fluid its examination in the laboratory was begun.

The cell-count was done on a Fuchs-Rosenthal slide with the fluid previously stained with a 0.5 per cent. solution of brilliant cresyl-blue, by adding one drop of the stain to ten of fluid and agitating the tube thoroughly so as to ensure uniform distribution of the cells. A count of over 3 cells per cubic millimetre was considered abnormal and was held to constitute a pathological fluid.

A differential count of the cells was made by taking up the deposit with a fine pipette after centrifuging 3 c.c. of fluid at high speed, staining it with a drop of Unna-Pappenheim's methyl-green-pyronin stain and examining it as a wet preparation under a cover-slip. Where there was a high cell-count the slide was examined with

the dark-ground illumination for spirochaetes, but in no instance were any discovered. The cells recognized in doing the differential count were large and small lymphocytes (grouped together), polymorphonuclear leucocytes, large mononuclear cells (some with, and some without phagocytosed granules in their cytoplasm) and plasma cells. The results of the differential counts were not of very much importance from the point of view of the present investigation, because whenever abnormal cells were found the cell-count was also raised.

The total protein was estimated by Mestrezat's diaphanometric method and a reading of over 30 mg. per cent. was considered abnormal, though in the absence of any other abnormality a reading of over 35 mg. per cent. was required before the fluid was regarded as pathological.

Pandy's globulin test was performed; a very faint haziness was not considered abnormal.

The Kahn test was done on 3 c.c. of fluid concentrated in the usual manner with ammonium sulphate.

Lange's colloidal gold test was carried out in each case. The gold was prepared in the laboratory and titrated with oxyhaemoglobin by the method described by Patterson [9]; in this way very satisfactory results were obtained.

The cell-counts and the protein and globulin estimations were always carried out within a few hours of taking the fluid, and the Kahn and gold tests were always done within four days, the fluid being kept on ice in the interval. The only exception to the last condition being that of the cases at Yei, on the Belgian Congo frontier, as the fluids were brought to Khartoum in two days by air; but the cell and protein estimations were performed at Yei.

Fluids contaminated with blood were always discarded.

Grouping of cases.—For the purpose of comparison with available European figures the cases were grouped as follows:—

- (1) Chancre, no secondary lesions, blood-serum Kahn-negative.
- (2) Chancre, no secondary lesions, blood-serum Kahn-positive.
- (3) Secondary, with lesions of skin or mucous membranes; history less than six months.
- (4) Cases with lesions of skin or mucous membranes; duration of infection, six months to two years.
- (5) Latent tertiary, with no clinical lesions but Kahn positive; history over one year.
- (6) Active tertiary, with lesions of skin or mucous membranes; history over two years.

(7) Active tertiary, with gummata or visceral syphilis; history over two years.

(8) Congenital cases.

(9) With clinical signs of involvement of the nervous system.

(10) A group from Yei, in the Bahr-el-Ghazal Province.

Group 1.—Sero-negative primary. No nervous signs. Five cases; 2 with pathological fluids, 1 having increased cells and protein, and the other increased protein only; no hypertension.

Group 2.—Sero-positive primary. No nervous signs. Thirty-two cases; 12 with pathological fluids (= 37.5 per cent.), 9 having increased protein, 5 increased cells, 2 positive Pandy, 1 positive Kahn, and 1 a luetic gold curve without any other change; no hypertension.

Group 3.—Secondary, with skin lesions, less than six months' history; no nervous signs; sero-positive. Thirty-three cases; 14 with pathological fluids (= 42.4 per cent.), 12 having increased cells, 7 increased protein, 4 positive Pandy, 1 positive Kahn, 1 a weak gold curve; no hypertension.

Group 4.—Lesions of skin or mucous membranes; history, six months to one year; no nervous signs; sero-positive. Twenty cases; 7 with pathological fluids (= 35 per cent.), 5 having increased protein, 3 increased cells, 2 positive Pandy, 2 positive Kahn. None with a positive gold curve or hypertension.

Group 5.—Latent tertiary; history over one year; no nervous signs; sero-positive. One hundred and seventy-two cases; 36 with pathological fluids (21 per cent.), 25 having increased protein, 20 increased cells, 16 positive Pandy, 7 positive Kahn, 5 positive gold curves, and 1 with hypertension and positive Kahn.

Group 6.—Active tertiary, with lesions of skin or mucous membranes; history over two years; no nervous signs. Thirty-three cases; 12 with pathological fluids (= 36.6 per cent.), 9 having increased protein, 5 increased cells, 5 positive Pandy, 2 positive Kahn, 2 positive gold curves, and 1 with hypertension in addition to other abnormalities.

Group 7.—Active tertiary, with gummata or visceral syphilis; history over two years; no nervous signs. Thirty cases; 14 with pathological fluids (46.6 per cent.), 10 having increased protein, 4 increased cells, 4 positive Pandy, 3 positive Kahn, 3 positive gold curve and 1 hypertension (due, undoubtedly, to congestive heart failure, but associated with pleocytosis, increased protein and a weak paretic curve).

If one takes Groups 6 and 7 together, one has 63 cases of active tertiary syphilis, and of these 26 (41.3 per cent.) have pathological fluids.

Group 8.—Congenital. Seven under 2 years of age, without nervous signs, of whom 4 (57 per cent.) had pathological fluids, one with only $3\frac{1}{2}$ cells, having 5 per cent. of plasma cells in the differential count.

Nine between the ages of 11 and 20 years, of whom 1 had a third nerve palsy, with a normal fluid, and one had hypertension with a protein of 45 mg. per cent.; 3 others had positive fluids, making a total of 44 per cent. for this age-period.

Group 9.—With clinical neuro-syphilis. Twenty-seven cases, that is 6.75 per cent. of the 400 in the series, of whom 20 (74 per cent.) had pathological fluids. Kahn positive in the blood-serum.

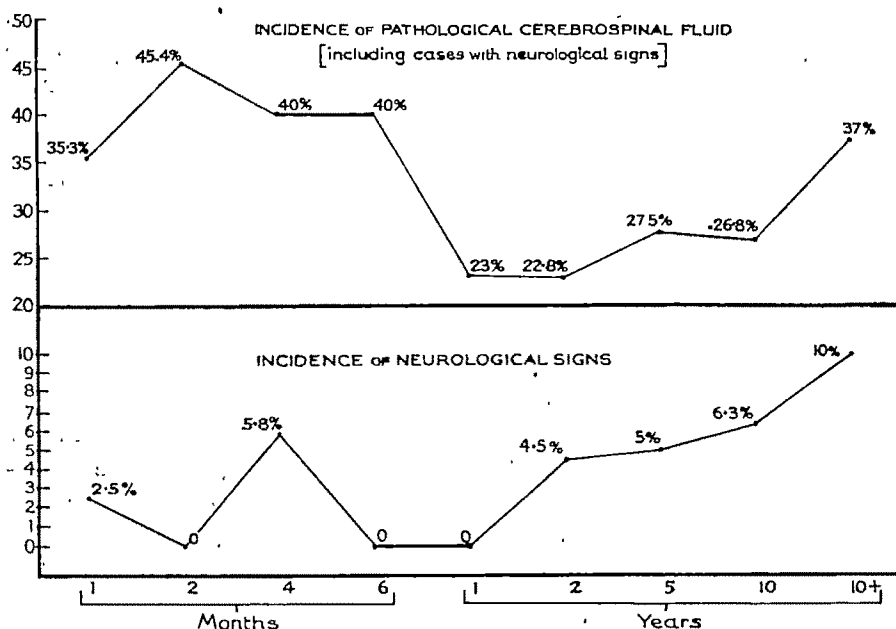


FIG. 1.

Group 10.—Cases from Yei, in the Bahr-el-Ghazal Province, where syphilis has only recently been introduced.

The subjects of this investigation were members of some negro tribes on the border of the Belgian Congo. Yaws used to be very prevalent in the neighbourhood, but its place is now being taken by syphilis.

The series includes twenty with large crusted circinate or rupia-like skin lesions, mucous patches and condylomata of less than six months' history; of these three had pathological fluids (15 per cent.) but no signs of nervous involvement. Five cases had gummatous ulcers of

six months' to two years' duration, including one (20 per cent.) with a pathological fluid, and one of the three tertiary cases of about five years' duration had a positive fluid, all without any neurological signs.

Among the twenty of less than six months' duration were six children, between the ages of 18 months' and 6 years, who had apparently been infected by contact with their parents, in much the same way as those reported by Hudson and Nægelsbach. One infant of 4 months was said to be congenitally infected, and was a mass of crusted sores; its fluid was normal.

The incidence of pathological fluids and of neurological signs can best be appreciated by presenting the figures in the form of a graph (fig. 1), showing the case percentages for different periods in the course of the disease. This estimate does not include the group of cases from Yei. It will be seen that the curve for pathological fluids shows a high peak in the secondary stage, as one would expect, and then falls for a period of four or five years, till the tertiary manifestations begin to be evident. The irregular form of the curve for neurological signs during the first four months is due to paucity of cases; the 2.5 per cent. at one month represents one case only.

In comparing these findings with those recorded in Europe and America, among white races, one has to exercise great care to ascertain that the same standards are used. The large series of Fordyce and Rosen [10] is not admissible for comparison since they include in their figures a considerable number of patients who were known to be neuro-syphilitics and were referred to the authors by other practitioners; this invalidates their figures as far as they are held to represent an estimate of the nervous lesions in the syphilitic population.

TABLE I.—AVERAGE FINDINGS FROM THE LITERATURE OF THE INCIDENCE OF CHANGES IN THE CEREBROSPINAL FLUID WITHOUT CLINICAL NEURO-SYPHILIS, COMPARED WITH THE FIGURES FROM THE SUDAN.

Stage of disease			Percentage with pathological cerebrospinal fluid	
			European and American	Sudanese
Sero-negative primary	..	..	9.6	10*
Sero-positive primary	..	..	19.4	87.5
Secondary ..	..	..	81.6	42.4
Active tertiary	..	..	85.8	{ Early 35
Latent tertiary	..	..	82.9	{ Late 41.3
Congenital†	..	..	27	{ Early 57
				{ Late 44

* Only 5 cases.

† In the case of the congenital syphilitics these figures include those with neurological signs and serve as an indication of general involvement.

The reports of twenty-one different authors [11-29] have been carefully selected and their figures in some instances slightly revised, where the necessary data were given, so as to reduce them all to approximately the same standards as are used in the present work. The averages calculated from the total figures for each group are recorded in the first column of Table I for comparison with the Sudanese figures.

Estimates of the incidence of clinical neuro-syphilitic affections are not easy to find; Kolmer [30] considers that gross disease occurs in 10 per cent. of all cases of syphilis (presumably he means when they are untreated) and that minor signs of involvement of the nervous system might be found in between 10 and 20 per cent. Mattauschek and Pilcz in their survey of 4,134 syphilitic Austrian army officers found 4·8 per cent. developed paresis, 2·7 per cent. tabes and 3·2 per cent. cerebrospinal syphilis—a total incidence of 10·7 per cent.

The twenty-seven cases with clinical signs of neuro-syphilis in the present survey of the Sudanese (6·75 per cent. of the total) include only one case that may possibly be considered a primary neuronc degeneration; all the others are of the vascular or inflammatory type, so it appears that the incidence of cerebrospinal syphilis, as distinct from the para-syphilitic degenerative lesions, is rather higher than in Europe.

Discussion.—One would hesitate to suggest that the finding of a higher incidence of cerebrospinal fluid changes in the early stages of syphilis in the Sudanese means that their central nervous systems are more often invaded than are those of white races, for it is obvious that such changes are only an indication of meningeal inflammation, and it is quite possible for spirochaetes to lodge in the brain without provoking such a reaction; indeed it is the question of the reaction provoked by infection that is of supreme importance in the present discussion.

It will be seen that after the period of secondary invasion the incidence of changes in the cerebrospinal fluid sinks to the level obtaining in white races, and that in the latent tertiary phase it is even lower.

The nature of the lesions which give rise to clinical signs of nervous disease is particularly interesting. In the present series there are seven cases of cerebral syphilis; three with myelitis giving rise to paraplegia; one which was probably a gummatous meningitis; a variety of vascular and meningitic lesions, including one Herxheimer reaction; and only one of primary neuronc degeneration, a case of optic atrophy, as opposed to a gummatous or definitely inflammatory lesion. These observations are borne out by the experiences of other medical men in the Sudan, and they are paralleled by the findings of Webb and Holliday in Buganda.

It becomes evident that the florid reaction to infection in the skin is not the only feature which distinguishes the disease in these people; a precisely similar response is provoked in the nervous system.

It has been suggested by Arzt and Fuhs among others, that there may be an antagonism between cutaneous lesions and disease of the central nervous system, but cutaneous lesions evidently do not prevent a meningeal reaction in the secondary stage, and it is much more reasonable to visualize a rather exaggerated cellular response throughout the whole body than to suppose that the brunt of the invasion is borne by the skin.

The relatively high incidence of nervous lesions (6.75 per cent.) occurring in this series makes it impossible to explain the absence of para-syphilitic degenerations as being a result of shielding of the nervous system from invasion; it can only be due to a difference in cell immunity. Inasmuch as such an immunity may be acquired while the secondary skin lesions are in evidence, one is justified in postulating some relationship between these two phenomena.

When one reviews the history of the progress of syphilis in Europe one is struck by the changes which have taken place in its manifestations since the days when it was known as the "great pox." In England to-day skin lesions and gummatous diseases of the nervous system are far less common, but general paralysis and tabes have arisen to take their place. Kanner [31] says that general paralysis did not appear in Europe till 1670, some 170 years after the supposed introduction of syphilis. It seems that general paralysis is now occurring more frequently than hitherto in the negroes of the United States (Foster [32]) and that in some districts the incidence in the asylums is considerably higher among the coloured than among the white admissions. In Japan it seems that general paralysis has been greatly on the increase during the past thirty years. Kanner considers that syphilis runs a definite course in a community, starting with an inflammatory phase as evidenced by gummatous lesions, which gradually dwindles in intensity while a degenerative or para-syphilitic phase takes its place; he goes further than this and quotes the extreme rarity of general paralysis among the North American Indians as representing a still later phase where almost complete immunity has been achieved by the race. If that notion of the evolution of the disease in a community be correct, one would expect to find during the next ten or twenty years a decline in the incidence of para-syphilitic affections in Europe, but, unhappily, should this occur the credit would undoubtedly be claimed by those who organized anti-syphilitic treatment.

The importance of the part played by endemic malaria in preventing general paralysis has been lessened by the discovery (Nägelsbach) that in the mountainous districts of Western Abyssinia, where malaria is unknown, syphilis behaves just as it does in the Sudan and parasymphilitic lesions do not occur; further, there is now considerable evidence that the coincidence of malaria with syphilitic infection does not protect the subject from subsequent general paralysis; Mandl and Puntigam [33] quote sixteen cases from the literature where general paralysis or tabes have occurred in patients who had spontaneous malaria at various periods after their primary syphilitic infection, and report a further four cases of general paralysis, two of taboparesis, and nine of tabes similarly occurring; parallel instances are reported by Gougerot [34], Richter [35], and Schwartz [36]. That malaria may modify the course of a syphilitic infection, even apart from its acknowledged effect when used therapeutically in general paralysis, cannot be denied; there are now many records of gummatous lesions appearing during malarial treatment and Wilson [37] has described a series of brains of persons dying after such treatment in whom changes of a proliferative inflammatory nature had appeared instead of the milder neuronc degeneration that is held responsible for general paralysis. The belief that a neurotropic strain of the spirochæte exists, or that the ill-effects of civilization upon the nerve-cells are ætiological factors in the production of general paralysis is too controversial a matter to discuss here, but neither seems to have much evidence to support it.

It would seem most satisfactory to explain the absence of parasymphilitic affections in the Sudanese as a result of an actual cell immunity acquired in the early stages of the disease. The exaggerated reaction which is accountable for the skin lesions may be considered, in part at any rate, as an allergic phenomenon. In tuberculosis, allergy is held responsible for many of the more spectacular cellular reactions, and it seems fair to make a comparison in the case of syphilis. The relation between the achievement of an allergic state and the presence of immunity in syphilis is a matter that requires much investigation. Particularly, as in tuberculosis, is it important to determine whether allergy is essential to immunity; upon the answer to that question depends the whole controversy on the subject of early intensive anti-symphilitic treatment.

SUMMARY.

The results of a neurological survey of 400 syphilitic Sudanese is reported. Routine examination of the cerebrospinal fluid showed a high incidence of abnormality. Clinical nervous disease was present in

6.75 per cent.; it consisted of gummatous or vascular lesions in most cases, and there was only one that was possibly a primary optic atrophy.

In the discussion it is suggested that the absence of para-syphilitic infections is due to an acquired cell immunity, associated with an allergic state, and the occurrence of such a reaction is interpreted as a stage in the development of syphilis in the community.

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BIBLIOGRAPHY.

- [1] LACAPÈRE, G. *Rev. de Méd. et d'Hyg. Trop.*, 1931, **4**, 23, 196.
- [2] RAYNAUD, M., LACROIX, BÉRAUD, M., et BOUTIN, P. *Bull. Soc. franç. Dermat. et Syph.*, 1926, **139**, 88, and *ibid.*, 520.
- [3] WEBB, W. L., and HOLLIDAY, M. *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1927, **39**, 21.
- [4] HUDSON, E. H. *U. S. Nav. Med. Bull.*, 1928, **26**, 817.
- [5] NAGELSBAUGH, E. *Arch. f. Schiff. u. Trop. Hyg.*, 1926, **30**, 121. Reviewed in *Bull. Hyg.*, 1926, 867.
- [6] HERMANS, E. H. *Acta Leidensia (Scholæ Med. Trop.)*, 1927, **2**, 196.
- [7] FEBRUCCIO. *Arch. Ital. Sci. Med. Colon.*, 1928, **9**, 785.
- [8] HEWER, T. F. *Lancet*, 1932, **1**, 1042.
- [9] PATTERSON, J. *Brit. Journ. Exper. Path.*, 1931, **12**, 148.
- [10] FORDYCE, J. A., and ROSEN, I. *Journ. Amer. Med. Assoc.*, 1921, **77**, 1696.
- [11] SCHOU, H. J. *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1923, **81**, 418.
- [12] FÖRTIG. *Arch. f. Dermat. u. Syph.*, 1926, **149**, 627.
- [13] FLISCHMANN, R. *Deutsch. Zeitschr. f. Nervenkrank.*, 1921, **70**, 177.
- [14] KIRCHBERG. *Ann. de Mal. Vén.*, 1928, **28**, 561.
- [15] MILLS, C. H. *Brit. Med. Journ.*, 1927, **2**, 527.
- [16] FIELDS, P., PARNELL, R. J. G., and MATTLAND, H. B. *Med. Res. Council Rep.*, 1919, No. 45.
- [17] CORNAZ, G. *Journ. Nerv. and Ment. Dis.*, 1919, **49**, 282.
- [18] WITK, C. *Bram*, 1917, **40**, 408.
- [19] WILK, U. J., and MARSHALL, C. H. *Arch. Dermat. and Syph.*, 1921, **3**, 272.
- [20] KONRAD, J. *Arch. f. Dermat. u. Syph.*, 1930-31, **162**, 102.
- [21] FINGER and KYRLE. *Ibid.*, 1922, **138**, 41.
- [22] SARATZANO, E. F., et alia. *Ann. des Mal. Vén.*, 1928, **23**, 481.
- [23] ARZT, L., and FUHS, H. *Arch. f. Dermat. u. Syph.*, 1927, **153**, 227.
- [24] *Idem.* *Ibid.*, 1924, **148**, 252.
- [25] *Idem.* *Ibid.*, 1929, **157**, 841.
- [26] *Idem.* *Ibid.*, 1931, **163**, 164.
- [27] SAMSON, K. *Monatschr. f. Kinderheilk.*, 1927, **36**, 16.
- [28] TRENER, O. *Ibid.*, **35**, 398.
- [29] JEANS, P. O., and SCHWAB, S. I. *Arch. Paediatr.*, 1923, **40**, 462.
- [30] KOLMER. "Treatment of Syphilis." 1926, p. 999.
- [31] KANNER, L. *Amer. Journ. Syph.*, 1927, **11**, 28.
- [32] FOSTER, R. H. *Amer. Journ. Psychiatr.*, 1926, **5**, 681.
- [33] MANDL, A., and PUNTIGAM, F. *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1931, **133**, 196.
- [34] GUGEROT, M. H. *Bull. Soc. franç. Dermat.*, 1927, **34**, 234.
- [35] RICHTER, W. *Deutsch. med. Wochenschr.*, 1928, **54**, 222, 264.
- [36] SCHWARTZ. *Münch med. Wochenschr.*, 1924, **71**, 618.
- [37] WILSON, R. B. *Bram*, 1928, **51**, 440.

CEREBRAL INVOLVEMENT IN HEAD INJURY.¹

A STUDY BASED ON THE EXAMINATION OF TWO HUNDRED CASES.

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INTRODUCTION.

UNDER the auspices of the Statistical Research Department, I have had the opportunity of studying the cases of head injury admitted to the surgical wards of Edinburgh Royal Infirmary.

The condition of the cases on admission, the stages of recovery, the changes in the cerebrospinal fluid, and the condition some months after discharge, have been the main lines of investigation. In order to make the records suitable for statistical study, I have carried out the clinical investigations according to a scheme drawn up in the form of a printed questionnaire. This paper is therefore an analysis of the clinical features of two hundred consecutive case records compiled according to a uniform scheme by one observer.

Historical.—Interest in the pathology of head injuries has been stimulated by the recent increase in knowledge of intracranial physiology. The investigations of Cushing [7], [8], Dandy [10], Weed [37] and Kubie [17] have shown how the cerebrospinal fluid is formed and how it circulates, and have demonstrated to some extent the mechanism of its re-absorption into the blood-stream. They have also shown the striking effects which can be produced on the cerebral tissue by means of the intravenous injection of hyper- and hypotonic solutions.

A degree of cerebral oedema is a constant complication of severe head injury in which contusion of the brain has occurred, and this has led to the assumption (Trotter [36], Jackson [15], Rand [27], &c.) that the occurrence of cerebral oedema is a dangerous complication to be countered by powerful measures. Treatment of head injuries at the present time tends to be directed largely, if not entirely, towards the reduction of cerebral oedema and intracranial pressure.

The work of Foerster and Penfield [12], [26], based on experimental and human material, has shown the scarring of the brain which follows injury. From the clinical side, these changes have been investigated by

¹ Based upon a thesis submitted for the degree of M.D. Edin., March, 1932.

encephalographic studies, one of the most notable of which is that of Bielschowsky [4].

Trotter [34] considers that unresolved contusion of the brain is the cause of most post-concussional symptoms, and emphasizes the importance of applying the present-day knowledge of intracranial physiology towards reducing any cerebral œdema which may be present, and in this way allowing the contused areas to recover.

From the neurological point of view, however, the clinical study of head injury has received relatively little attention, and offers a wide field for investigation.

ANALYSIS OF CLINICAL MATERIAL.

The following tables show the age and sex incidence of the cases, and classifies them according to the cause of the injury.

TABLE I.—AGE AND SEX INCIDENCE.

Age-period	Male	Female	Total
0-10 years	16	7	23
10-20 "	34	5	39
20-30 "	53	5	58
30-40 "	20	4	24
40-50 "	18	7	25
50-60 "	8	3	11
60-70 "	10	4	14
Over 70 "	2	4	6
Totals	161	39	200

In this and all subsequent tables, the figures represent the number of cases, unless otherwise stated.

TABLE II.—CLASSIFICATION ACCORDING TO THE CAUSE OF INJURY.

Cause of Injury	Male	Female	Total
Motor car collision ..	3	3	6
Motor cycle collision ..	40	0	40
Pedal cycle collision ..	18	1	19
Knocked down in street	28	29	57
Fall	44	6	50
Other cause	20	0	20
No record	8	0	8
Totals	161	39	200

TABLE III.—TABLE SHOWING THE RELATION OF THE TYPE OF THE ACCIDENT TO THE AGE AND SEX.

Age-period	Motor car	Motor cycle	Cycle	Knocked down	Fall	Other causes	No record	Totals
0-10 years ..	0	0	0	11	11	0	1	23
10-20 " ..	1	6	12	6	6	5	8	39
20-30 " ..	1	27	5	10	8	6	1	58
30-40 " ..	1	6	0	5	8	3	1	24
40-50 " ..	1	1	1	10	9	2	1	25
50-60 " ..	1	0	1	2	3	8	1	11
60-70 " ..	1	0	0	8	4	1	0	14
Over 70 " ..	0	0	0	5	1	0	0	6
Totals ..	6	40	19	57	50	20	8	200
Male	3	40	18	28	44	20	8	161
Female	3	0	1	29	6	0	0	39

Analysis of these three tables brings out the following facts:—

(1) The incidence of head injury reaches its maximum between the ages of 20 and 30 years.

(2) The large number of cases occurring at this period is principally accounted for by motor cycle accidents.

(3) At all age-periods up to the age of 70, the incidence among males is much greater than that among females. This is due to the fact that the motor cycle and pedal cycle accidents are almost entirely confined to males, as also are the industrial accidents. The latter are mostly classified as being due to a "fall" or to some "other cause" (Table II).

(4) Apart from the injuries due to motor car collisions, of which there are very few in the series, the only type of accident in which the female incidence is as great as the male is that in which the injury is due to the patient having been knocked down in the street.

(5) The incidence in children under 10 years of age is over twice as great in males as in females. As these accidents to children were due almost entirely to falls, or to the child being knocked down in the street (Table III), the preponderance of males is probably due to the greater development of an adventurous tendency in that sex.

In a few instances, some physical defect shown by the patient contributed to the occurrence of the accident.

Classification of cases.—The classification of cases of head injury has been attempted in many ways and the question as to which is the best method is one of some difficulty. In the first place, cases are often classified according to the damage to the skull. By a second method

an attempt is made to classify the damage to the brain as well as to the skull. This method of classification is used by Bagley [1].

A method such as this is of little use from the clinical point of view. Many cases would fall into several of the groups, and many of the groups have reference rather to post-mortem findings than to clinical observations.

It is generally admitted that the degree of damage to the skull gives no definite indication of the degree of damage to the brain. It appears, therefore, desirable to adopt a classification which will provide an indication of the degree of damage to the brain as well as to the skull. The only way to achieve this is to classify each case under two headings: (1) The damage to the skull; (2) the damage to the brain.

The first of these will not be considered here, as it is mainly a radiological problem.

With regard to the second heading, there are few types of cerebral damage which it is possible to diagnose accurately during life. As will be shown later, the whole of the brain suffers in severe head injuries, and it seems to be more satisfactory to refer clinically to the degree of cerebral injury in general terms, such as slight, moderate or severe, except in those cases in which gross signs, such as hemiplegia, indicate that one part of the brain has suffered excessively.

As Symonds [32] suggested, *the duration of loss of full consciousness* has been used in the present series as the indication of the degree of cerebral injury. While this seems to be the most useful method to follow, it does not always provide an accurate estimate of the degree of cerebral damage. It must be borne in mind, for example, that the duration of unconsciousness may be increased by the supervention of a complication, such as hæmorrhage, which is not necessarily dependent on the degree of cerebral contusion.

In using this classification, it is necessary to consider what are to be accepted as the criteria for full return of consciousness. The usual stages of recovery are somewhat similar in all degrees of injury, though the duration of the stages of recovery varies greatly. They may now be conveniently described.

Stages of recovery.—Immediately after the blow the whole of the nervous system may be paralysed; even the respiratory and cardiac movements may cease. If recovery is to occur, the heart and respiration recommence. Involuntary movements of the limbs then occur, and the reflexes return. Speech returns with a few words or phrases and movements become more purposeful. Up to this stage it is mainly

the lower mechanisms of the brain that are recovering, and the similarity between cases is great. The higher cerebral functions, however, differ in every individual, and the stages of recovery of these functions produce widely different clinical pictures. The mental condition may simulate any of the states seen in alcoholic poisoning; in both conditions the clinical picture probably depends on the individual psychological structure and balance. Thus the patient may be drowsy or talkative, docile or aggressive, impudent or irritable. He is never reserved; he may tell you his secrets, may be boastful or affectionate, and may even attempt to bribe his attendants to let him out of bed.

Then, comparatively suddenly, he looks round and asks where he is. He has now recovered full consciousness and returns to his normal behaviour and treats those who are looking after him with the customary civility. These changes indicate that the higher functions of control and inhibition have again taken charge of his behaviour. These are the first to be affected in alcoholic poisoning and are the last to recover after a head injury. They presumably constitute the most sensitive mechanisms in the brain. These stages of recovery may be traced not only in the more severe cases, but also in those in which the individual is unconscious for a few minutes only.

It is sometimes difficult to determine at what stage consciousness has fully returned, and indeed in some severe cases the individual is never again able to carry out the same mental processes as were possible before the accident. In this series, the patient was not considered to have recovered full consciousness unless he was fully orientated and able to answer questions intelligently. He should, for example, be able to describe clearly what he last remembered before the accident and what he first remembered after it. The victim of an accident may be able to move and even, to talk sensibly and yet have no subsequent memory of his words or actions. This is a familiar state of affairs; as, for example, when a football player is able to continue the game after a head injury and subsequently have no recollection of it. This failure to commit his actions to memory would indicate, according to the scheme here used, that he had not recovered consciousness in full. Such a patient may answer simple inquiries not unnaturally and yet be found on cross-examination to be disorientated as regards time and place. It is, therefore, apparent that *the evidence of untrained observers as to when full consciousness returns is of little value*. How then can this duration of unconsciousness be estimated? In the state of full consciousness any occurrence in which the patient is actively or passively

concerned makes an impression on the memory, and can be subsequently called to mind. It has accordingly been found that the patient's subsequent memory of when he woke up provides a not inaccurate indication of when consciousness returned. By this indication, the duration of loss of consciousness can be estimated with fair accuracy even when the patient is seen for the first time long after the accident.

Grouping of Cases according to Duration of Loss of Consciousness.

The cases of the series have been divided as follows:—

Group "A" were unconscious for less than 1 hour	80 cases
Group "B" were unconscious for from 1 to 24 hours	57 "
Group "C" were unconscious for more than 24 hours	47 "
Group "D" comprised the fatal cases	16 "

The different groups A, B, C and D, are repeatedly referred to throughout the text, without further explanation.

TABLE IV.—TABLE SHOWING THE RELATION OF THE AGE-PERIODS TO THE DEGREE OF CEREBRAL DAMAGE. THE PROPORTION OF FATALITIES IN EACH AGE-PERIOD IS ALSO SHOWN.

Age-period	Group				Totals	Percentage died
	A	B	C	D		
0-10 years ..	10	2	10	1	23	4.4 per cent.
10-20 " ..	19	18	6	1	39	2.6 "
20-30 " ..	20	18	18	2	58	3.4 "
30-40 " ..	8	10	5	1	24	4.2 "
40-50 " ..	18	6	8	3	25	12.0 "
50-60 " ..	6	1	1	3	11	27.0 "
60-70 " ..	3	6	1	4	14	28.6 "
Over 70 " ..	1	1	3	1	6	16.7 "
Totals ..	80	57	47	16	200	8.0 per cent.

Table IV shows that, after the age of 40, the percentage of fatal results rises greatly, and correspondingly the number of cases in Group C becomes proportionately much less than in the earlier years. This probably indicates that as age advances the individual becomes progressively less able to withstand the effects of severe injury, and this explanation is supported by the fact, as will be shown later, that full recovery of cerebral function after a head injury is much less likely to occur in the old than in the young.

The mortality rate of the series is 8 per cent., but cases which died within twenty-four hours of admission are not included in the series.

Fracture of the skull.—The following table (Table V) gives the

proportion of cases in each group which showed evidence of fracture of the skull. The evidence was considered certain when the fracture was clearly shown either on X-ray examination, or at operation or at the post-mortem examination.

TABLE V.

	Group				Totals
	A	B	C	D	
Certain evidence of fracture ..	16	12	27	8	63
No certain X-ray or other evidence of fracture	51	85	7	2	95
Totals	67	47	34	10	158
Percentage of cases which showed a fracture	24 per cent.	26 per cent.	80 per cent.	80 per cent.	40 per cent.

While many cases in all groups present certain evidence of fracture of the skull, the proportion is much higher in Group C and D (80 per cent.) than in the less severely injured cases of Groups A and B (24 and 26 per cent. respectively).

Cases in which injuries to other parts were also present.—Injuries to other parts were present in sixty-three cases. Such injuries may divert attention from slight concussion, and a proportion of these cases are found to be classified in hospital records without reference to a head injury, although the latter had been of sufficient severity to cause loss of consciousness. If, after an accident, the victim does not remember the details of how it happened, up to and including the moment in which he was injured, it is probable that he has suffered from concussion, and careful inquiry of the first thing he remembered after the accident will often show that consciousness was lost for a few minutes. It is a matter of importance that the possibility of head injury in such cases should not be overlooked.

Temperature, pulse and respiration.—Immediately following a severe injury both respiratory movement and heart action may cease. Where recovery occurs respiration recommences, but often remains feeble and shallow, especially where shock is marked. The pulse is also feeble and rapid. Shock is a constant feature of severe head injury, and during this stage the temperature is subnormal.

As recovery progresses, the temperature rises, the pulse becomes slower and the respirations deeper. In the more severe cases the

temperature rises a degree or two above normal and the pulse wave becomes forceful—the so-called hard pulse. Thereafter, in most cases the temperature, pulse and respiration return to normal in the course of a few days.

Some points of importance emerge from a study of the temperature, pulse and respiration charts. In attempting to draw conclusions from the clinical charts, I have excluded those belonging to cases in which there were either injuries to other parts of the body or gross laceration of the scalp.

Charts of cases in Group A.—Of forty-six cases in Group A which were suitable for study, twenty-one showed no temperature record above 98·4° F. In the remainder, the temperature on one or more occasions rose above this level, but in no case above 99·8° F. In only six cases was the temperature above normal on admission. In the remaining nineteen cases the rise occurred from twelve to twenty-four hours after the accident, the first temperature records taken being subnormal.

In only ten cases out of the forty-six was there any abnormality in the pulse-rate at any time after admission. In these ten the rate was increased during the first or second day, but the increase in rate was rarely above 15 per cent. of what was later seen to be the normal for that individual.

Charts of cases in Group B.—Twenty-two cases in Group B were suitable for study. In nine of these no temperature record above normality was found. In the remainder the records were, on the average, a little higher than in Group A, but never above 100·2° F. As in Group A, the temperature was usually subnormal on admission and rose during the ensuing twenty-four hours. A definite rise in pulse-rate was apparent in all except three of the twenty-two cases. It was, as a rule, associated with a rise of temperature, but in some cases the pulse-rate was highest on admission when the temperature was low and shock was present. A slight increase in the rate of respiration (10 to 20 per cent.) was present in twelve cases during the first day or two days.

Charts of cases in Group C.—Thirty cases in this group were suitable for study. In only two of these did the temperature remain below 98·4° F. In nineteen the temperature did not exceed 100° F., but in nine temperatures between 100° F. and 101·8° F. were recorded. As was the case in Groups A and B, the temperature was usually subnormal on admission. In this group, however, the readings did not, as a rule,

return to normal within forty-eight hours, as was usually the case in Groups A and B, but often continued high for several days.

While, as in the other groups, a degree of acceleration of the pulse-rate may be present, there is in many cases in this group some slowing of the pulse-rate during the first ten days. This is probably due to the development of increased intracranial pressure. A slight increase in the respiratory rate (10 to 30 per cent.) was recorded in twenty of the thirty cases.

If the pulse-rate during the last few days in hospital be taken as normal for the individual, the patients in this group often had abnormally low pulse-rates at some period during the first ten days of their illness. Only eleven of the thirty cases failed to show this feature, and in those in which it was present the pulse-rate was often 30 to 40 per cent. below the normal, that is to say, a pulse-rate of 50 would occur in an individual with a normal rate of 80.

Charts of cases in Group D. (The fatal cases.)—A study of the charts of fatal cases is of special interest. Ten of these were suitable for investigation. As the mortality is much higher in the older age-periods than in the younger, there are relatively fewer of the older cases in Group C, as not many survived injuries of the severity incurred by the cases in that group.

The striking feature in the charts of Group D is the progressive increase in pulse-rate; there is no stage of reaction with a hard slow pulse. On the contrary, the pulse increases steadily in rate and becomes progressively more feeble, and with it the respiratory rate also increases. In most cases the reaction from the initial shock is sufficient for the temperature to rise, and death may occur with hyperthermia. In some, however, the temperature never rises above normal.

In cases below the age of 30 it was found that, if the initial shock was survived for twenty-four hours, death seldom occurred, unless some complication, as meningitis, supervened.

The condition of the pulse is therefore an important prognostic guide. A slowing and hardening of the pulse-wave may be welcomed in severe cases, but a tendency for the pulse to become progressively more rapid and feeble is a sign of grave prognostic significance.

There is no evidence from the study of these charts that increased intracranial pressure contributed to a fatal issue. The rapid and feeble pulse is quite unlike that which occurs in conditions of increased pressure. Immediate and delayed shock seems to play a part in the fatal result in these cases as in cases of severe injury to other parts of the body.

ANALYSIS OF SYMPTOMS AND SIGNS IN HEAD INJURY.

In the following analysis it will be noted that in some of the cases there is no record of certain of the symptoms and signs which are studied. The omission of any record of certain symptoms was due usually either to an abnormal mental state of the patient, or to the patient being a young child unable to answer questions. The most frequent reason for the omission of notes regarding certain signs was the presence of injuries to other parts of the body. For example, a fracture of the lower extremity often prevented examination of the reflexes.

Headache.—The following table compares the degree of headache complained of in the four groups of cases.

TABLE VI.

Degree of headache			A	B	C	D	Totals
Severe	..	..	18	17	22	4	61
Moderate	..	..	26	15	6	1	48
None	..	..	32	34	8	0	64
No record	..	..	4	1	11	11	27
Totals	..	..	80	37	17	16	200

Apart from the cases in which the pain was referred to the site of the injury, the headache usually took the form of a dull frontal pain, often throbbing in nature, of the type associated with increased intracranial pressure.

Complete absence of headache in cases of both slight and severe injury was not uncommon. As will be shown later, the degree of headache is to some extent proportional to the increase of intracranial pressure.

The pain may continue for only a few hours, but in some cases causes distress for days, months or years.

Vomiting.—Vomiting occurs not infrequently. In cases in which presence or absence of this symptom was reported it occurred as follows.

TABLE VII.

Vomiting			Group				Totals
			A	B	C	D	
Present	..	..	26	19	21	6	72
Absent	..	..	47	35	11	4	97
Totals	..	..	73	54	32	10	169

Vomiting of altered blood was common in cases in which hæmorrhage from the nose and pharynx was present, blood being swallowed reflexly while the patient is unconscious. If however, coma is so profound that even this reflex is abolished, there is a risk that blood may be aspirated into the lungs if the patient is nursed in such a position that blood from the nose will gravitate into the pharynx.

No significance, apparently, can be attached to the occurrence of vomiting. It occurred in many cases of all groups. It rarely continued for more than two days after the injury, and in many cases it occurred on only one or two occasions.

Fits.—In three cases a fit was reported to have occurred. This happened at a varying interval after the injury. In cases (of which there were two) in which the convulsion developed within a few hours of the injury, it was presumably caused by the irritative effect of hæmorrhages into the brain substance or perhaps over the surface of the brain.

Fits may also occur some days after the accident, as in the following case.

P. C., a male, aged 33, was knocked down by a motor car. He recovered consciousness after an interval of four days, but was then found to have some aphasia. He was easily confused, and the naming of objects was particularly difficult. Nine days after the accident he began to have tonic spasms of the right hand followed by clonic jerkings of that extremity. One fit, which I observed, lasted for thirty seconds. These recurred several times a day for five days. Thereafter he improved steadily, but when examined nine months later still complained of being unable to remember words. This was very noticeable if he attempted to tell a story.

These Jacksonian attacks undoubtedly indicated some damage to the left cerebral hemisphere. There was no evidence of increased intracranial pressure, and this, combined with the persistent difficulty with speech, was suggestive of damage within the brain substance.

EXAMINATION OF CRANIAL NERVES.

Smell.—Anosmia is a not uncommon sequela of a severe head injury. It is usually recognized by the patient himself after full return of consciousness. Damage to the filaments of the olfactory nerve may be caused by *contre-coup* injury, as was probably the mechanism of injury in the following case.

O. R., a male, aged 32, was thrown from his motor bicycle and struck the right parieto-occipital region. A fracture of the skull in this situation resulted,

and he lay unconscious for seven days. Thereafter his sense of smell was entirely lost though it had formerly been very acute. A severe degree of loss of memory and mental ability indicated extensive damage to the brain.

Vision.—Visual acuity is probably diminished temporarily after all severe injuries, but loss of vision is seldom a lasting complaint.

Damage to the optic nerve or chiasma in fractures of the base of the skull may cause complete blindness in one or both eyes, or may produce temporal field defects if the optic chiasma is injured.

A. R., a male, aged 36, was admitted unconscious, there having been no witness of the accident. Though deeply unconscious on admission, he was fully conscious when examined twelve hours later. There was severe bruising of the frontal region with extensive effusion into the periorbital tissues. On examining the eyes, no direct reaction of the left pupil to light could be obtained, while the consensual reaction of the left, and direct reaction of the right, were normal. The right pupil was 5.5 mm., and left 4.4 mm. in diameter. There was complete blindness in the left eye and no subsequent recovery occurred. The visual acuity of the right eye after the swelling had subsided was $\frac{6}{6}$, but a marked loss of the visual field was present, especially in the lower temporal quadrant (fig. 1). No improvement in this defect had occurred eight months after the accident.

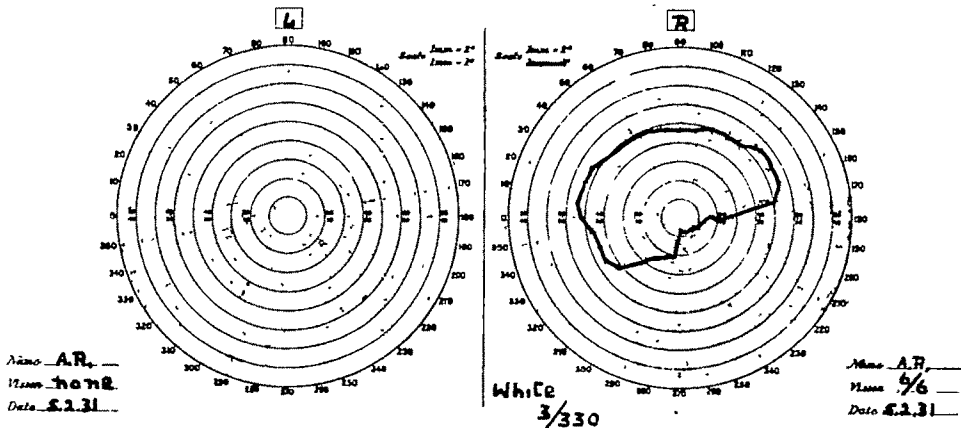


FIG. 1.

Increased intracranial pressure, when present, may cause papilloedema. This was observed in only two cases; in both it developed several days after the injury, and later disappeared spontaneously.

Ocular nerves.—The pupils were unequal in thirty-eight cases. In only three of these was there clinical evidence of greater damage to one side of the brain than to the other. On the other hand, in twenty cases

in which changes in the reflexes suggested that there was more damage to one side of the brain, the pupils were equal in all but two.

Gross paralysis of the ocular movements is uncommon, but a slight degree of oculomotor disturbance, as evidenced by diplopia, is not infrequent, and was observed in six cases. These oculomotor disturbances may be due either to damage to the oculomotor nerves, or to bruising of the mid-brain. They usually disappear in the course of a few days or weeks, but may be permanent.

In one patient a considerable increase of intracranial pressure developed which caused paralysis of the sixth cranial nerve on one side.

E. Y., a woman, aged 22, was knocked down in the street by a motor car. She recovered consciousness in about forty-eight hours but continued to suffer from severe headaches. Six days after the accident there developed a weakness of the outward movement of the right eye, which, in the course of a few days, became a complete external rectus paralysis. No signs of localized pressure on the brain by hæmorrhage could be made out, but a slight degree of papilloedema developed, and the cerebrospinal fluid pressure was 330 mm. of water. She continued to have severe headache for a month and diplopia for three months. After that period, however, she improved steadily and when examined six months after the accident, had fully recovered.

Seventh cranial nerve.—Facial paresis or paralysis may be present in cases of basal fracture associated with hæmorrhage from the ear. It was found in six cases, in all of whom there had been bleeding from the ear on the same side. Complete recovery in the course of a few weeks is the rule.

Eighth cranial nerve.—In basal fractures associated with hæmorrhage into the middle ear, some deafness may occur. It is usually of the middle-ear variety.

W. M., a male, aged 22, was involved in a collision while riding his motor bicycle. There was hæmorrhage from the right ear and from the nose. There was no apparent injury to the scalp, but X-ray examination showed a fracture of the right temporal region. Weakness of the right side of the face was observed on the day following admission, and when consciousness returned two days later a complete peripheral paralysis of the right side of the face was demonstrated. There was some loss of the sense of taste over the anterior part of the right half of his tongue.

By the right ear he heard spoken voice at one foot, by the left ear whisper at four feet. The Weber test was not referred, but bone conduction in the right ear was greater than air conduction. The patient returned to work eight weeks after the accident, but when examined eight months after admission was suffering from headache and dizziness. The facial paralysis had recovered, but deafness

in the right ear was worse than when in the ward. The tuning-fork tests gave the same result. He also complained of a constant hissing noise in the ear.

There was no question of compensation outstanding.

Evidence of damage of the 5th, 9th, 10th, 11th or 12th cranial nerves was detected in no case.

MOTOR FUNCTIONS AND REFLEXES.

From the practical point of view, examination of the motor functions is carried out in order to determine whether one side of the brain is more disturbed than the other, and especially to ascertain whether the functioning of one cerebral hemisphere is being *progressively* impaired, as may occur through hæmorrhage continuing after the accident. The development of weakness or paralysis of one side of the body coming on gradually after the injury must always indicate a complication of this kind.

Bilateral extensor plantar responses are not uncommonly found when the patients are first examined, as is shown in Table VIII. They are more common in the severe cases and during the stages of unconsciousness.

TABLE VIII.—PLANTAR REFLEXES IN CASES EXAMINED WITHIN TWENTY-FOUR HOURS OF ACCIDENT.

Group	Both Flexor	Both Extensor	One Flexor and One Extensor
A	46	2	5
B	28	3	4
C	17	14	3
D	8	10	2
	94	29	14

Cases in which the physical examination indicated that one side of the brain was more damaged than the other.—In fourteen cases changes in the reflexes indicated that one pyramidal tract had been more damaged than the other. Hæmorrhages into the brain-stem are relatively uncommon, and one can usually assume that any damage to the pyramidal tract is caused within the cerebrum, and, therefore, if more marked on one side, that one cerebral hemisphere has been more severely injured than the other.

In this connection it must be borne in mind that the side of the

brain which is most severely damaged bears no constant relationship to the side of the skull which receives the injury. This is shown in the two following case records:—

Blow to the Right Side of the Skull causing Left-sided Hemiplegia.

A. G., a female, aged 26, was knocked down by a motor car and immediately rendered unconscious. When examined five hours later, she was found to have a bruise and cut in the right parietal region. She was deeply stuporose. There were free movements of the right arm and leg, but no movement of the left upper and lower extremities could be elicited. There was also paralysis of the left side of face. A period of over two weeks elapsed before she recovered consciousness. During that period the cerebrospinal fluid was found to be normal and to show no increase of pressure. The dura mater was exposed by operation just in front of the wound, but no hæmorrhage could be found. Seven weeks after the accident she still had a marked degree of spastic hemiplegia.

Blow to Right Side of the Skull causing Right-sided Hemiplegia.

M. McM., a male, aged 35, was knocked down by a motor car and immediately rendered unconscious. He remained deeply stuporose until his death four weeks later. During the whole of that period there was complete loss of power of the right upper and lower extremities, whereas there was no apparent weakness of the left side. At the post-mortem examination a depressed fracture of the right parieto-occipital region was found. The cerebral tissue below the site of fracture showed little evidence of damage, but the *contre-coup* injury was so extensive that a large part of the left hemisphere was destroyed.

Abnormal movements.—The presence of abnormal movements, such as tremor or athetosis, was not observed as a feature of the acute stage.

In one case of great severity muscular twitchings were observed, which simulated closely those seen in uræmia. The circulation at the time was very poor, which suggests the possibility that inadequate nutrition of the nervous elements was the cause of the condition.

Rigidity of the neck muscles.—A sign which was often present was rigidity of the neck muscles. It was often present when Kernig's sign was absent. It was found to a slight degree in thirty-eight cases, and to a marked degree in twenty-eight. This sign was present in cases in which meningitis developed, but might also be an indication of sub-arachnoid hæmorrhage, which is a common result of severe head injury. On thirty-two occasions in which the cerebrospinal fluid was found to contain a uniform and marked admixture of blood (over 1,000 r.b.c. per c.mm.), the neck muscles showed some rigidity, except in one patient

who was deeply comatose and dying. The degree of rigidity in subarachnoid hæmorrhage is often so pronounced that the diagnosis of meningitis is apt to be made. Rigidity of the neck muscles may also be produced by the presence of a bruise in the neighbourhood of the neck or occipital region. The rigidity when marked is usually associated with a degree of neck retraction, which, as in meningitis, is more pronounced in children than in adults.

TABLE IX.

Neck rigidity	Group				Totals
	A	B	C	D	
None	58	36	6	6	109
Slight	18	12	18	3	41
Marked	2	9	20	3	28
No record	7	6	5	4	22
Totals	80	57	47	16	200

The frequency with which neck rigidity was noted is shown in Table IX. The large proportion of cases in Group C which show this sign to a marked degree is a striking feature of the table.

Blood in the cerebrospinal fluid usually disappears in the course of three or four days. Neck rigidity also ceases to be present at about the same interval after the injury. In the following table the amount of blood in the cerebrospinal fluid in case E.Y. and the degree of neck rigidity are compared (Table X).

TABLE X.—CASE E.Y.

Interval after injury at which lumbar puncture was carried out	Red blood corpuscle count per c mm.	Degree of neck rigidity
16 hours	90,000	Marked
3 days	10,000	Slight
5 days	130	None
8 days	0	None

It may be concluded that the neck rigidity often present after severe head injury is usually associated with subarachnoid hæmorrhage.

Disturbances of the sphincters.—Loss of control of the sphincters is a usual accompaniment of unconsciousness, whether resulting from head injury or other cause. Retention of urine is an important complication in the severe cases of head injury and often leads to great restlessness.

It was present in several cases and should be examined for as a routine in all severe head injury cases.

Higher cerebral functions. Retrograde amnesia.—In the series of cases investigated, recollection of the actual blow to the head was never present when immediate loss of consciousness had resulted. One woman remembered being struck by the motor car which knocked her down, but in that case it was the fall to the ground which injured the head, and of this fall she had no recollection. After return of consciousness, it was found in all cases that there was an interval, immediately preceding the injury, of which the patient had no recollection. The duration of this interval, the period of *retrograde amnesia*, was inquired into carefully in ninety-six cases. In sixty-nine cases its duration was only one or two seconds, in twenty-four cases it lasted several minutes, while in only three cases was it of longer duration than half an hour. This interval was estimated by questioning the patient after full return of consciousness. If questioned before this, the interval of loss of memory before the accident was of considerably longer duration.

In the following table the duration of retrograde amnesia is compared to the groups into which the cases fall.

TABLE XI.—APPROXIMATE DURATION OF RETROGRADE AMNESIA.

Group	A few seconds	1 to 30 minutes	Over 30 minutes
A	35	4	0
B	28	8	1
C	6	12	2
	69	24	3

The longer periods of retrograde amnesia are therefore more commonly found in cases which fall into Group C.

The recollection of events shortly preceding the accident may usually be taken as an indication that full consciousness has returned.

The question as to when a patient should be considered to have regained complete consciousness is a point of medico-legal importance which would arise in cases such as the Merritt trial [30]. From my experience of head injury cases, I feel justified in asserting that if an individual after a head injury is able to describe correctly events which preceded loss of consciousness by only a few minutes or seconds (as did Mrs. Merritt), consciousness has then returned in full.

In states of confusion, disorientation and altered personality which

may occur before full consciousness returns, the patient has no recollection of events shortly preceding the accident. When, however, memory of events preceding the accident was present, it was never found, in the present series, to be other than accurate. This point, which is of medico-legal importance, was recently emphasized by Somerville [31].

With regard to events following the accident, the patient's ideas may be permanently inaccurate. This is well shown by Somerville's case of a boy who incorrectly concluded that the doctor, whom he remembered attending to him after his injury, had caused the accident. This case was used in the Merritt trial, as providing evidence that the recollection of events preceding the injury may be inaccurate [30]. It is, however, apparent that this case provides no evidence in favour of this possibility. The boy's belief was entirely due to his *faulty interpretation while recovering consciousness*, and had no connection with his actual memory of events preceding the accident. In point of fact, as Dr. Somerville subsequently explained, the boy remembered nothing of what occurred after he left his home ten minutes before the accident occurred. That is to say, he had a complete retrograde amnesia for a period of ten minutes.

Stages in the recovery of consciousness.—The stages of recovery of consciousness, and particularly of the mental and speech functions, are of great interest and may repay detailed study. The following case record provides a typical illustration of the steps towards recovery in a case of severe head injury.

R. D., a shepherd, aged 27, was admitted to hospital on May 3, 1931, having been thrown off his motor cycle. When examined a few hours later there was no severe shock. He was bleeding from the right ear and was tossing restlessly in bed. He made no attempt to speak and was in a deeply stuporose condition.

May 4, 1931.—Owing to violent restlessness he was transferred to the ward for incidental delirium, where he had to be strapped in bed. He powerfully resisted any interference and seemed very sensitive when the plantar reflexes were being examined. There was little or no attempt to speak.

May 5, 1931.—To-day he was fighting hard against the straps which held him down and calling out loudly without using any definite words.

May 9, 1931.—He greeted me cheerfully with "Good morning, sir," and shook hands. He talked cheerfully about having to get home to-night. Much of what he said was meaningless, but a few sentences were intelligible. He gave his name correctly, but in reply to a question said, "I've been here two years." Sentences often begun correctly, later became meaningless. "Here, could I go out into the . . ." He almost wept when prevented from

getting up, and seemed very annoyed. "Well, I'll come back again," he would say impatiently. "That's no kind of way to . . . now don't you think it." Then, sitting up and waving his arms about, he would argue vehemently but quite meaninglessly with the attendant, and wept when again prevented from getting up.

Plantar reflexes were to-day flexor, whereas they had been previously extensor on both sides.

May 19, 1931.—He was very talkative and emphasized all he said with powerful gestures. His condition was very like that of a talkative and intoxicated person. He argued that he must go home, and boasted freely of his great skill at shearing sheep and catching trout. He promised to give money to the Sister and examiner if they would let him go. He talked incessantly and repeated his arguments over and over again. Most of his sentences were coherent, but a few were meaningless. Like a man who is intoxicated, he paid little or no attention to what was said to him, and would not listen to reason. He had no knowledge of where he was and absolutely no comprehension of his condition. After considerable persuasion he would respond to a simple request, such as "Put out your tongue."

May 25, 1931.—He was quite changed. He remembered being troublesome in the ward and was now very apologetic. He said he felt very well and strong enough to start work again. He knew where he was and why he was there, and had a normal understanding of his environment. There was no repetition of his former unbalanced talk. He listened to and appreciated all that was said to him. He could now recollect certain events preceding the accident. He remembered driving along the road at a speed of about 35 miles an hour, anxious to get home before dark, and remembered actually colliding with the tar barrel which caused his accident.

Thereafter this patient's recovery was uneventful. When seen seven months later he was physically fit; but his doctor said he was much less reserved than before the accident. He had now no recollection of hitting the tar barrel but remembered events clearly to within a few minutes of the accident. He was unable to remember the number of sheep he counted about six hours before the accident, but otherwise he could find no fault with his memory.

I have made several detailed records of the recovery of speech in cases such as the above and have found that they show remarkable similarity. At first all words are impossible. The first attempt to articulate usually takes the form of a groan or a shout repeated frequently. Then a few words are occasionally uttered. These may be meaningless, but soon a few common phrases are correctly produced. These are often repeated frequently and are usually shouted out loudly. The patient's vocabulary gradually increases. Common phrases are at first all that can be said, but gradually speech becomes more intelligible. There is still, however, a lack of any power of

understanding or reason. The patient's incessant talk is mainly repetition. He pays no attention to what is said to him and is quite disorientated. The inhibitions and social training which prompt the average patient to speak with respect to the nurses and doctor are among the last functions to recover, so that he is often impudent to and familiar with his attendants. Subsequent to this stage the recovery of insight, orientation and the usual social habits rapidly follows, and the patient recovers full consciousness and begins to think about events preceding his accident.

Examination of the cerebrospinal fluid.—Examination of the cerebrospinal fluid was carried out on sixty-seven occasions in forty cases. Persistence of severe headache or of unconsciousness was considered to justify lumbar puncture.

I performed lumbar puncture in these cases with the patient lying on his side, the head and spine being on the same level. A fine needle was used and the pressure of the fluid was in most cases measured by Greenfield's manometer. Fluid can be removed very slowly as the rate of flow can be accurately controlled by means of the tap on the needle.

The cases in which lumbar puncture was performed all suffered with severe injury, as in the slighter cases there was no indication for performing the operation.

Taking readings above 200 mm. of water pressure as being above normal, out of the 49 readings made the pressure was increased in 30. In only 9 instances, however, was the pressure above 330 mm.

In the following table each pressure estimation is compared with the mental state at the time of lumbar puncture.

TABLE XII.

Mental state	Cerebrospinal fluid pressure (millimetres of water)				Total
	0 to 100	100 to 200	200 to 300	Over 300	
Normal	1	8	10	2	16
Confused	2	3	7	1	13
Stuporose	2	5	4	6	17
Comatose	0	3	0	0	3
Totals	5	14	21	9	49

It is at once apparent from a study of this table that there is no relationship between the degree of unconsciousness and the fluid pressure. On twelve occasions the cerebrospinal fluid pressure was above 200 mm.

of water in cases in which consciousness had fully returned, while on seven occasions in which the pressure was below 200 mm. of water, the patient was stuporose; and in three deeply comatose patients, all of whom died a few hours after lumbar puncture, the pressure was in no case above 200 mm.

This table, therefore, indicates that the depth of unconsciousness is not an index of the degree of intracranial pressure.

The pressure in uncomplicated cases, however, may provide some indication of the degree of cerebral oedema present. Jefferson [16] has recently emphasized that when severe head injuries are operated on several days after the accident, the brain is often found to be shrunken and dehydrated, even though the patient is still deeply stuporose. This surgical observation may explain the low pressure readings in several deeply unconscious patients shown in the above table.

These observations justify the following conclusions:—

(1) A certain increase of intracranial pressure often develops after head injury.

(2) This increase of pressure is seldom great.

(3) The degree of intracranial pressure is not proportional to the mental state of the patient.

A comparison between the cerebrospinal fluid pressure and the presence of headache at the time of lumbar puncture.—In order to attempt to find the cause of the severe headaches which may follow head injury, a comparison has been made between the cerebrospinal fluid pressure and the degree of headache. In some cases that were deeply unconscious the presence of headache could not be determined. On thirty occasions, however, an accurate comparison could be made, as is shown in the following table:—

TABLE XIII.

Degree of headache	Cerebrospinal fluid pressure (millimetres of water)				Totals
	0 to 100	100 to 200	200 to 300	Over 300	
Nons	1	1	3	1	6
Moderate	0	2	4	0	6
Severe	1	1	12	4	18
Totals	2	4	19	5	30

From this table it is seen that in 90 per cent. of the cases in which headache was severe the cerebrospinal fluid was above its normal pressure, that is, the pressure rose above 200 mm. of water. The

figures unfortunately are small, but even so they probably indicate that if severe pain in the head develops after injury to the skull a considerable increase of intracranial pressure is present. It is important to distinguish between pain due to local injury to the scalp or skull and pain due to increased pressure. The character of the increased pressure type of headache in these cases is that of a dull, throbbing or bursting type of pain, usually felt mainly in the frontal region. It is aggravated by stooping and is often relieved to some extent by raising the level of the head relative to the rest of the body.

From these observations it is probable that the presence of severe headache of the type described indicates that the intracranial pressure is raised.

Quantity of blood in the subarachnoid space.—If in carrying out lumbar puncture care be taken to penetrate the dura mater once only, and to pierce it for the least necessary distance, contamination with blood does not occur, except in a degree so slight as to be discerned only on microscopical examination of the fluid. In most of the cases, both a red and white cell count of the cerebrospinal fluid were carried out within an hour of taking the specimen. In all specimens in which blood was present, it was found to be evenly mixed with the fluid withdrawn and, on standing, the supernatant fluid was yellow in colour.

In making a cell count, the specimen was first thoroughly shaken, and, according to the degree of blood contamination, the red cell count was carried out on either the ordinary blood-cell counting slide, or on the Fuchs-Rosenthal chamber. When the blood contamination was very great, it was necessary to dilute the specimen in a blood-counting pipette before carrying out the count.

It is well known that in cases of spontaneous hæmorrhage into the cerebrospinal fluid, such as may occur in a case of leaking cerebral aneurysm, the initial dramatic onset of severe pain in the head is often followed, after a varying interval, by loss of consciousness. This may be partly brought about by increased intracranial pressure, but there is little doubt that it is largely due to alteration of the chemical constitution of the cerebrospinal fluid through the admixture of blood. It is found, for example, that the pressure of the fluid in these cases is often not greatly raised. Further, in fatal cases, the clinical picture is unlike that of death from increased intracranial pressure, but resembles more nearly the type of death seen after severe head injuries. The experimental work of Bagley [2] has recently shown that in dogs the subarachnoid injection of blood from the animal itself may produce

widespread irritative effects, including loss of consciousness and convulsions. It is not surprising, therefore, to find that in those cases of head injury in which the amount of blood in the cerebrospinal fluid is great, loss of consciousness is always deep. This is shown in the following table :—

TABLE XIV.—BLOOD IN CEREBROSPINAL FLUID. (Red Blood Corpuscles per c.mm.)

	0 to 1,000	1,000 to 100,000	100,000 to 500,000	Over 500,000
<i>Mental State—</i>				
Normal ..	11	6	0	0
Confused ..	6	7	0	0
Stuporose ..	2	13	4	0
Comatose ..	0	1	0	2
<i>Headache—</i>				
None ..	5	2	1	0
Moderate ..	2	1	0	0
Severe ..	9	8	2	0

These figures suggest that a large quantity of blood in the sub-arachnoid space may cause, of itself, loss of consciousness. It must be borne in mind, however, that excessive subarachnoid hæmorrhage is often an indication of severe cerebral laceration, which would also produce prolonged unconsciousness.

The table also compares the degree of headache with the amount of blood contamination, but the comparison provides no evidence of relationship between the two.

The rate at which the blood is removed.—There were only a few cases in the series in which I felt justified in carrying out repeated lumbar punctures. Four examinations were, however, performed in case E.Y. and in case H.B., and three in case J.C. In each of these cases, the red blood corpuscle count, the white blood corpuscle count and the total protein content of the cerebrospinal fluid were plotted against the interval after injury at which lumbar puncture was performed. The results are shown in figs. 2, 3 and 4, and the rapid disappearance of the blood is a striking feature of all three charts. Not only so, but the rate of disappearance is remarkably constant, in each case there being relatively very few red blood-cells present seventy-two hours after the injury. A further point which is apparent in the curves from cases H.B. and J.C. (figs. 3 and 4), cases in which the fluid was examined on three consecutive days, is that the reduction of the red cell count between the first and second examination is approximately

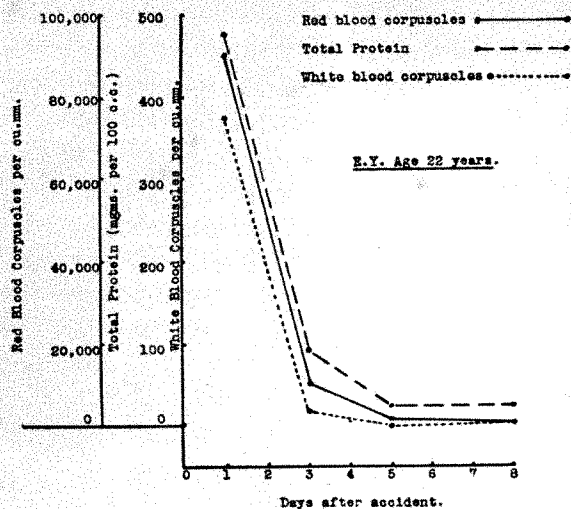


FIG. 2.

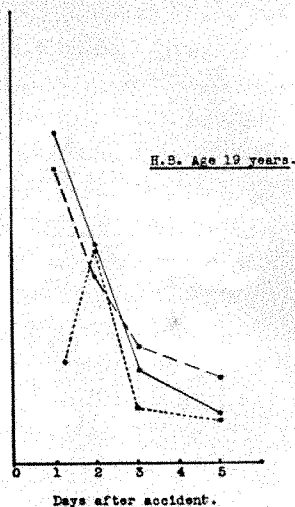


FIG. 3.

To show the rate at which the cerebrospinal fluid returns if normal.

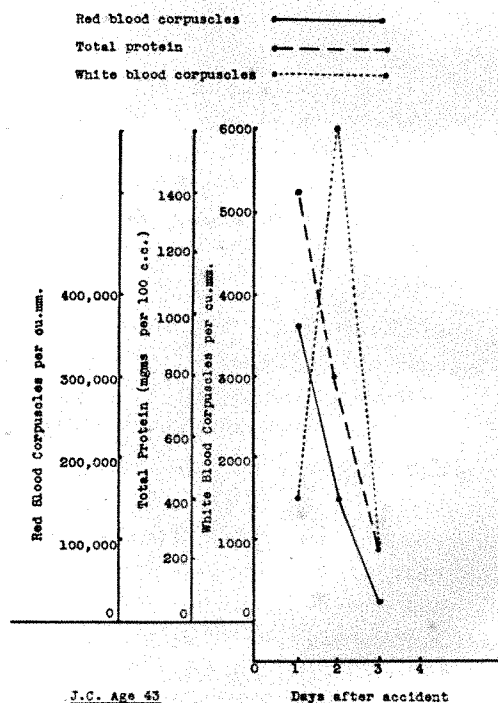
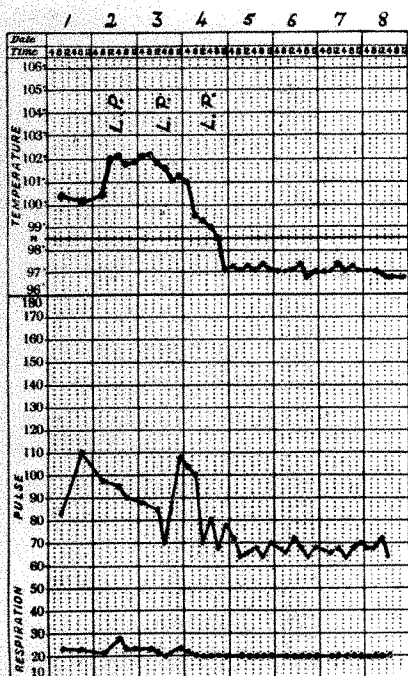


FIG. 4.—Case J. C. Showing the clinical features of meningitis in the second and third days of the illness.

equal to the reduction in the cell count between the second and third examination. Thus the curve for that period in both cases approximates closely to a straight line, and the observation suggests that the mechanism for removing the blood-cells operates at a constant rate. It is, however, assumed in discussing these cases that no further hæmorrhage occurred after the first twenty-four hours following injury. If, as in one case, a large quantity of blood (50,000 cells per cubic millimetre) is found in the fluid at an interval of seven days after the injury, it is probable either that hæmorrhage continued for some time after the accident, or that a fresh hæmorrhage occurred at an interval after the injury. This latter is a well-recognized complication and is described as Delayed Hæmorrhage or *Spätaoplexie* [5, 29].

The following case record provides an example of this complication:—

W. G., a male, aged 17, was found unconscious on the road beside his bicycle. He recovered consciousness after an interval of several hours. He continued, however, to suffer from headache and was found to have marked neck rigidity. Lumbar puncture was carried out two days after admission and the fluid was found to be deeply blood-stained. Relief of headache immediately followed lumbar puncture, and ten days later he was discharged free of symptoms.

A month after discharge he was readmitted with recurrence of severe headache. For a period of six days thereafter he was in a stuporose state and the headache continued unabated. Lumbar puncture was then performed, deeply blood-stained fluid was again drawn off and, as before, relief of headache occurred immediately. Recovery thereafter was uneventful, and when examined seven months later he had no complaint except of an occasional headache.

As the blood-cells disappear from the spinal fluid, the latter becomes brown in colour, as in Froin's syndrome. This yellow or brown coloration disappears in a few days after the blood-cells have been removed. In case E.Y., for example, the fluid was clear and yellow on the fifth day, but three days later, on the eighth day after the injury, was quite colourless.

Clot formation.—The development of a clot in a specimen of cerebrospinal fluid provides the most delicate indication available of the presence in the fluid of fibrinogen [13]. There is no tendency for blood in the cerebrospinal fluid to clot unless it comes in contact with damaged tissues. In one fatal case in this series, G.H., the red cell count in the fluid was actually 1,400,000 per cubic millimetre, and yet no tendency to clot was apparent in the specimen after allowing it to stand for half

an hour. In all cases of meningitis a clot develops, and indeed the development of a clot is always suggestive of infection having occurred.

Total protein content.—The total protein content of the fluid withdrawn was in most cases estimated in the Biochemical Laboratory. The specimen was thoroughly shaken before the test was carried out, and the Microkjeldahl method was used.

Figs. 2, 3 and 4 show that the fall in the protein content paralleled closely the fall in the red cell count. In fig. 2, for example, the protein content by the fifth day was only 18 milligrams per 100 cubic centimetres, that is to say it had fallen to normal in this short period. These observations are of interest from the point of view of the mechanism by which the blood is removed. If the red cells underwent lysis before their constituents were removed, the protein content would not be expected to fall so rapidly as it does in these cases. It therefore seems more likely that phagocytosis of the red cells is the essential part of the mechanism for removal. The endothelial cells lining the subarachnoid space, ventricles and choroid plexuses are all phagocytic (Hurst [14]), and they are no doubt responsible for the removal of the erythrocytes. I have often observed blood-pigment in these lining cells in post-mortem material derived from cases in this series. I have not, however, seen any sections in which the actual occurrence of phagocytosis could be demonstrated.

White corpuscles.—The white cells were counted on the Fuchs-Rosenthal slide, using toluidine blue as a stain, and acetic acid to dissolve the red cells.

The number of white cells present in the cases examined could, in uncomplicated cases, be accounted for largely by the hæmorrhage itself. Where this was the case, the white cells usually disappeared as rapidly as did the red cells. This was apparent in the cases E.Y. and H.B. (figs. 2 and 3). A rise in the white cell count is an early sign of an inflammatory reaction. This may be merely a mild aseptic type of meningitis, but may of course be due to a virulent pyogenic infection.

Case J. C. showed the features of an aseptic meningitis. For over forty-eight hours after admission the patient had a high temperature and pronounced rigidity of his neck. At the end of this period a second lumbar puncture was carried out (fig. 4), and the white cell count was found to have risen to 6,000 per cubic millimetre. In the course of the next twenty-four hours, however, the temperature dropped to normal, and the white cell count fell to 800 per cubic millimetre. The red cells and protein disappeared as in cases E.Y. and H.B. (figs. 2 and 3). Recovery thereafter was uneventful.

A rise of the white cell count in the cerebrospinal fluid is the earliest sign of a developing infection. This is illustrated by case A.G. which is referred to below.

Estimation of sugar.—The quantity of sugar in the blood is raised considerably after severe head injury, and glycosuria is not uncommon. It is therefore not surprising to find that the sugar content of the cerebrospinal fluid may also be high. Case A.G. is of interest in this connection. The head injury was very severe, and two days after the accident the blood contained 222 mg. of sugar per 100 cubic centimetres. On the day following, the cerebrospinal fluid contained as much as 130 mg. per 100 cubic centimetres, while there were practically no white cells in the fluid. This patient developed an infection of the middle ear, which had been damaged by a basal fracture, and gradually developed a fatal meningitis. Fig. 5 shows how early in the

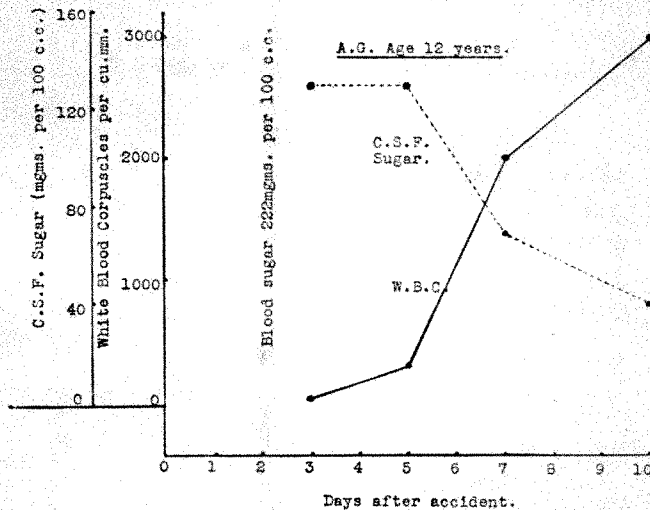


FIG. 5.—Case A. G. Showing the changes in the white corpuscle count and in the sugar content of the cerebrospinal fluid when meningitis was developing.

case evidence of the development of this infection became apparent in the cerebrospinal fluid. The rise in the white cell count and the fall in the sugar content are striking features. The rise in the white cell count was the first sign of threatening infection, and indeed this sign may be looked on as the earliest and most delicate indication of a commencing meningitis. The patient in this case survived for nineteen days after his injury.

The mechanism by which the brain is injured.—It is a remarkable fact that the skull, which contains a fragile structure such as the brain,

can be subjected to sudden blows of considerable severity without injury to the brain, especially in view of the fact that some movement of the brain relative to the skull may occur, as is evidenced by the occasional tearing of a cortical vein from its attachment to a venous sinus. Whether the head receives a blow or whether the head strikes the ground, the mechanism of cerebral injury is the same. The brain is obliged to undergo a sudden change in momentum, which, if the skull were not there to protect it, would cause its complete destruction. The fact that the brain fits the skull accurately is the main factor which enables the skull itself to bear the brunt of the blow.

The force applied to the skull in a case of concussion may be great and may be applied to only a small area of its surface. The force of the blow is, however, conveyed to the brain by the whole inner aspect of the skull on the side injured, and in this way is so distributed that the damage to any one part is correspondingly reduced.

Beyond violence of a certain degree, however, the brain also becomes damaged. Here again the effect is lessened by the force of the blow being distributed to all parts of the cerebrum. That a mechanism exists which distributes the strain to all parts, and so reduces the damage to any one part, is shown by the scattered capillary hæmorrhages which are often found throughout the brain of cases in which no gross cerebral contusion can be demonstrated.

Contre-coup injury.—It is largely through the tearing of small vessels in the pia arachnoid that hæmorrhage into the cerebrospinal fluid occurs. The bleeding is usually greatest at a point exactly opposite to that at which the injury is received. It seems that this so-called *contre-coup* injury, which is the most constant of all post-mortem findings in these cases, cannot be explained by any wave of force having been applied to the brain at that point. If we take, for example, the case of a man who falls on the frontal region on a hard surface, the momentum of the skull is arrested with great suddenness and the skull, in its turn, arrests the momentum of the brain in the manner described above. The force of the brain's momentum is directed towards making the brain continue its velocity in a downward (frontal in this case) direction. The occasional tearing of a cerebral vein provides conclusive evidence that some movement of the brain relative to the skull can take place. All parts of the brain are attempting to move in the same direction, and the maximum movement relative to the skull will be at a point opposite to the site of the frontal impact, viz., in the occipital region. It is I think apparent that the subarachnoid space is

the place of least resistance to this force. The combined forces of surface tension and intracranial pressure will prevent the spaces between the dura mater and skull, or the dura mater and arachnoid, being opened up. What then are the forces which prevent the space between the pia mater and arachnoid being forced open? In the first place there is the intracranial pressure which is slightly greater than atmospheric pressure, and in the second place there are the fine fibrous bands uniting the pia mater and arachnoid. The former force is the most important, but is somewhat lessened because, unlike the subdural space, it is possible for the subarachnoid space to enlarge without becoming a vacuum. This is because it can be filled with cerebrospinal fluid from other parts. Indeed the fact that brain tissue is heavier than the cerebrospinal fluid will tend to make the brain force itself downwards (forwards in this case) at the expense of the less heavy fluid, which will therefore tend to flow away from the site of impact.

Any such movement of the brain would be greatly lessened or abolished were the skull a closed box containing a constant volume of tissue and fluid. This doctrine of the skull being a closed box of this nature cannot, however, be accepted as correct; because in the first place, the volume of the brain can be greatly reduced by forcing blood away from it, and in the second place, the brain and cerebrospinal fluid have considerable room for expansion through the foramen magnum. I therefore suggest that the common *contre-coup* injury is caused by the brain tearing itself from its coverings by the force of its own momentum. The damage is therefore most likely to occur at that part of the brain which is opposite to the site of injury, though in very severe cases the injury may be much more extensive.

Should this be the correct explanation of the mechanisms by which *contre-coup* damage is produced, the type of injury found in this situation should be of a different nature to that found at the site of impact. This is precisely what actually occurs. At the site of injury some cerebral contusion may be apparent, the features of which are discoloration of the surface of the brain with small hæmorrhages within its substance. Hæmorrhage on the surface of the brain is, at the site of injury, absent or slight.

In the case of *contre-coup* injury, on the other hand, sub-arachnoid hæmorrhage is the chief and often the only sign. The arachnoid may be lifted up from the surface of the brain by a collection of blood. Extensive hæmorrhage may occur into the brain substance, but this is

merely an extension of hæmorrhage from the surface where the actual tearing of the vessels occurs. Examples of *contre-coup* injury are shown in figs. 6 and 7. The *contre-coup* damage usually appears to be much greater than the damage at the sight of injury, but this may be more apparent than real owing to its hæmorrhagic nature.

Mechanism of loss of consciousness.—The sudden loss of consciousness at the time of injury is considered by Trotter to be due to cerebral anæmia caused by a sudden flattening of the skull, what he terms

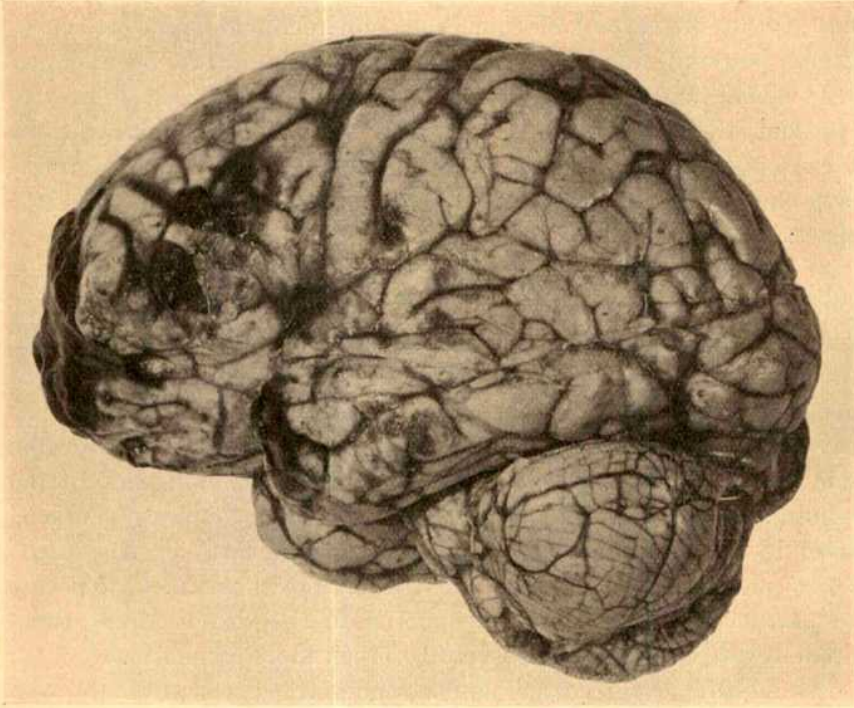


FIG. 6.—*Contre-coup* injury, showing sub-arachnoid hæmorrhage.

“Acute compressive anæmia” [35]. There are, however, difficulties in accepting this explanation. In the first place, the loss of consciousness is immediate and recovery is relatively slow. There are other conditions in which loss of consciousness is due to cerebral anæmia. Such may occur when a debilitated person suddenly assumes the erect posture. Loss of consciousness in this case is preceded by a feeling of light-headedness which lasts for a second or two, and in contrast to what happens after concussion, recovery of consciousness occurs completely as soon as the position of the head relative to the heart is adjusted by a

fall to the ground. Banking at corners in high-speed flying may produce the same effect, the blood being suddenly forced from the brain by its own momentum. In this case recovery of full consciousness occurs as soon as the sudden changing of direction is modified. A more prolonged period of cerebral anæmia occurs in a Stokes-Adams' seizure, in which the loss of consciousness is so prolonged that a convulsion often occurs, yet here again consciousness often returns as soon as the circulation is

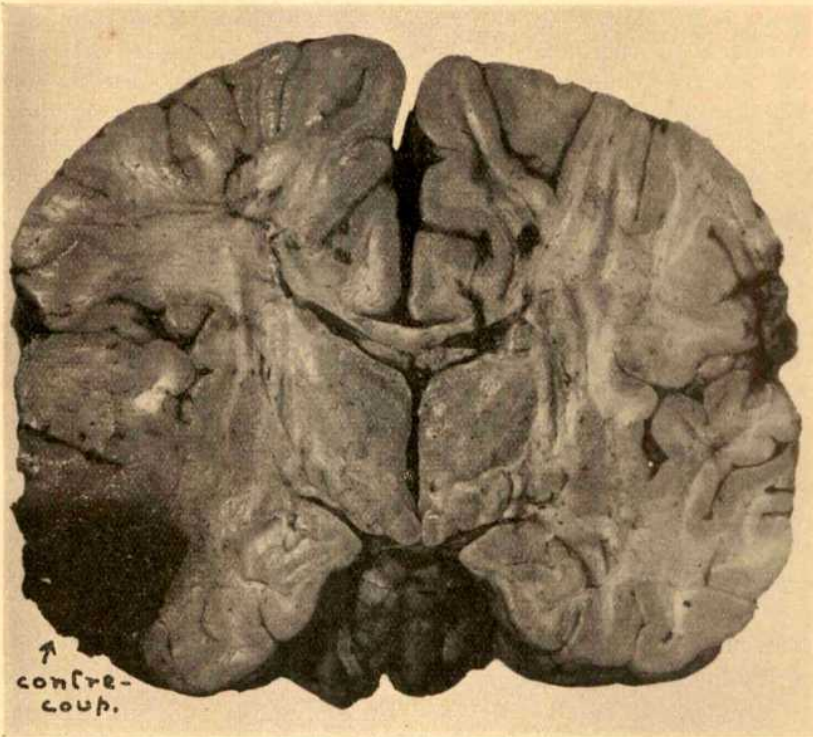


FIG. 7.—*Contre-coup* injury, showing extension of sub-arachnoid hæmorrhage into substance of the brain.

re-established. Further, the theory of an acute compressive anæmia does not explain why one patient should be unconscious for five and another for a period of thirty minutes. In the latter case, though the blow was presumably more severe, the duration of compression of the brain, should it have occurred, cannot have been of longer duration. Again, if loss of consciousness were due to cerebral anæmia, one would expect that in the very mild cases at least recovery of function would be rapid. We find on the contrary that recovery of full function of the

brain, even in the slightest injuries, is always a relatively slow process. Even in the mildest cases of concussion, those in which the individual does not lose the power of either walking or speaking, he remains in a dazed state for several seconds, during which time he gradually recovers his full mental powers.

The following case is of particular interest in this connection:—

W. R., a male, aged 34, had an accident while working in a mine on October 9, 1931. His head was crushed with considerable force between two hutches. This, however, did not cause him to lose consciousness immediately. He remembers all the details of the accident. He remembers sitting down after it occurred, while another worker bandaged his head. He remembers going up the pit shaft and entering the ambulance. Soon after entering the ambulance, however, he lost consciousness and did not regain his senses until in the Infirmary. When admitted, he had severe throbbing pains in his head. There was no visible fracture on X-ray examination and he was discharged a week later.

Soon after returning home he began to have "fainting turns" in which he would lose consciousness for a few seconds. No history of convulsions was obtained, but coincident with the onset of these turns pain in the head became severe and continued until he was admitted to Ward 32 under Professor Bramwell's charge on January 8, 1932. His complaint then was of severe and continual throbbing frontal pain and "fainting turns." He responded well to treatment with rest in bed and dehydration measures, and felt fit when discharged four weeks later.

In this case intracranial structures were sufficiently compressed and damaged to produce severe after-effects, yet no initial loss of consciousness occurred.

It would appear that the effect on the brain is not unlike the response of a peripheral nerve to an injury. Obstruction of all circulation to a nerve, as can be obtained by applying a sphygmomanometer armlet to the limb, fails to interrupt its functioning capacity except after many minutes. A sudden jar to the nerve trunk, however, causes an immediate interference with function, the severity and duration of which are directly proportional to the severity of the injury. Recovery of function is here, as in concussion, a relatively slow process. For these reasons it seems probable that the ancient conception of a commotion occurring in the nerve elements is the correct explanation of the sudden loss of consciousness. According to this view, the concussion of the nerve elements causes some molecular change which brings about a temporary interruption of function. That the myelin sheaths, at least, are easily disturbed by a sudden jar is demonstrated by the ease

with which slight carelessness in removing a spinal cord at autopsy will alter the myelin sheaths sufficiently to enable them to be stained by Marchi's method.

As has already been shown, the force of the blow received by the skull is distributed to all parts of the brain. After a severe blow to the skull, therefore, all parts of the brain must suffer to a greater or less degree. It is therefore not surprising that the site of the injury is of little significance in most cases. From whatever angle the skull is jolted or struck, the whole of the brain receives a certain degree of jarring, its whole mechanism is put out of action, and consequently consciousness is immediately lost. Consciousness cannot exist unless the association paths within the cerebrum are acting normally; hence any temporary interruption of conduction in the intracerebral fibres will cause immediate loss of consciousness. My conception of the mechanism of concussion is, therefore, that at the moment of injury the whole of the brain tissue undergoes mechanical agitation. This causes molecular disturbance within the nerve elements (probably in the myelin sheaths) which brings about an interruption in the conducting functions of the nerve-cell processes, and leads to the instantaneous loss of consciousness.

Types of injury.—It is interesting to consider the different types of head injury from the point of view of the degree of jar—or agitation, which they cause to the brain.

The degree of injury to the skull and brain must depend on:

(1) Rapidity with which the momentum of the brain and skull is altered.

(2) The degree of change of momentum. The momentum of a body depends on its mass and its velocity. The mass of the skull and brain is approximately constant, therefore the degree of injury must depend on: (a) the rapidity with which the velocity is altered; (b) the amount of change of velocity.

If, for example, the patient falls from a height on to a stone surface, both the above factors contribute towards the occurrence of a serious degree of brain damage.

(1) The velocity of the skull is arrested with great suddenness at the moment of contact with the hard stone.

(2) The velocity of the skull which is high at the moment of impact is completely abolished and may actually become negative if the skull rebounds. Hence the degree of change of velocity is great.

If, instead of a fall on a stone surface, the patient falls on soft grass, the amount of change of velocity is the same, but the suddenness of

change of velocity is much less owing to the softer surface. Hence the injury to the skull and brain is less severe.

Many cases have been described in the literature of the subject in which a pointed metal instrument has transfixed the skull and brain without consciousness being lost. This occurrence can be readily explained by the above conception. The point of the instrument being relatively sharp, a large part of its velocity is expended not in imparting velocity to the skull, but in penetrating its substance, and correspondingly the rapidity with which the skull is made to assume velocity is not inconsiderably lessened by this same factor. Any effort, so to speak, on the part of the instrument to impart a sudden velocity to the skull is prevented by the same effort causing further penetration of the skull by the metal instrument.

In the case of a moving object striking the head while at rest, the rapidity of the change of velocity of the skull and the degree of its change of velocity, depend on the momentum of the force which strikes it. As has already been mentioned, momentum depends on the two factors—the velocity of the object and the mass of the object. It therefore follows that a rapidly moving object and a heavy object, and especially one which possesses both these properties, will cause most damage to the brain.

Changes during recovery.—When consciousness is beginning to return and motor recovery has occurred, a stage of great restlessness and resistiveness is likely to supervene. This stage is often called the “stage of cerebral irritation” and is considered to be due to cerebral oedema, with a consequent increase of intracranial pressure. As has already been shown, however, the mental state is not in any way proportional to the pressure as estimated by the manometer; indeed, as already mentioned, seven stuporose cases which subsequently recovered showed a pressure within the limits of the normal. While the individual is very irritable in the popular sense of the word, there is no evidence that the condition is due to any mechanical irritation of the nervous elements. As Symonds [33] has pointed out, other pathological conditions which cause cerebral oedema, such as cerebral tumour and uræmia, do not produce a clinical picture in any way resembling this traumatic state.

The condition is seen in all degrees of concussion. The concussed football player often moves his limbs restlessly and talks meaninglessly, and not a few cases of head injury are violent and abusive when seen in the out-patient department. Though in slight injuries the duration of

this stage is brief when compared to what may be seen in severe cases, it seems that the condition has the same significance in both types of case. In this stage of irritability, consciousness is not fully recovered and the patients have no subsequent recollection of their actions. It is probable that these irritable states merely represent a stage in the recovery of consciousness. The mental and other higher cerebral functions have not yet recovered, and owing to the lack of their control the more primitive and less vulnerable motor activity is running wild.

Oedema and other circulatory disturbances are frequent complications of cerebral trauma, and their far-reaching effects must not be lost sight of. It seems improbable, however, that they are the cause of the sudden loss of consciousness, or that they provide the explanation of the condition called cerebral irritation.

RE-EXAMINATION OF CASES SOME MONTHS AFTER DISCHARGE FROM HOSPITAL.

The follow-up investigation is important, because it touches on the urgent questions of prognosis and ultimate rate of recovery.

As is well known, certain symptoms are liable to develop after head injuries. These have been described under such terms as post-concussional neurosis and the post-concussional syndrome, the chief features of which include headache, dizziness, nervousness, sleeplessness, inability to concentrate, and disturbances of memory and behaviour.

In order to attempt to elucidate some of the problems associated with this aspect of the subject, a series of cases have been re-examined at an average interval of six months after discharge from hospital.

Method of investigation.—Of the 184 cases which survived the injury, 141 were interviewed and examined at an average interval of six months after the accident; 55 of these had noticed no abnormal symptoms since discharge, while in the remaining 86 symptoms which were presumably due to the injury had been present since discharge. The proportion in the different groups is shown in the following table:—

TABLE XV.

	A	B	C	Totals
Symptoms since discharge ..	30	31	25	86
No symptoms ..	31	14	10	55
Total reporting..	61	45	35	141

ANALYSIS OF COMMON POST-CONCUSSIONAL SYMPTOMS.

In the study of symptoms it was considered advisable to exclude those in which there was any question of compensation outstanding. There were 14 such cases. The remaining 72 cases provide a valuable opportunity for studying post-concussional symptoms, and these are used exclusively in the following analyses.

Headache.—Some degree of headache was present in 41 cases. It was slight in 28, and severe in 13 cases (Table XVI).

TABLE XVI.

Degree of headache	Group			Totals
	A	B	C	
Severe ..	1	7	5	13
Slight ..	11	13	5	29
None ..	8	8	15	31
Totals ..	20	28	24	72

TABLE XVII.—AGE-PERIODS.

Headache	0 to 10	10 to 20	20 to 30	30 to 40	40 to 50	50 to 60	60 to 70	Over 70
Present	4	11	17	8	9	2	1	0
Absent	5	8	8	6	3	1	3	2

These tables show, in the first place, that the incidence of headache is higher in Groups A and B than in Group C, and, in the second place, that its frequency is higher in the early age-periods than in the later. Thus 59 per cent. of the cases below the age of 40 complained of headache, while the figure for the cases above the age of 40 is 40 per cent.

If pain in the scar of a scalp injury be excluded the type of headache was remarkably constant. It was a dull pain referred to the frontal and temporal regions, often throbbing in nature. It was usually worse when the head was lowered, as when the patient went to bed at night, but in many cases it was worse on waking in the morning. It was usually aggravated by physical exertion or by excitement. In some cases it could be brought on by shaking the head, and in not a few it was more noticeable in dull wet weather. A gradual reduction of the degree of

pain was the rule, but in some cases the headaches continued with considerable severity and were seriously incapacitating. In two cases who had previously suffered from migraine, these attacks ceased after the accident.

The following are typical examples of cases showing this symptom :—

J. B., a male, aged 19, collided with a motor lorry while riding a motor cycle. He suffered a fracture of the right parieto-temporal region and was unconscious for five days. Four months after discharge he had not returned to work because of severe pains in the head. These were frontal and throbbing, worse on rising in the morning and sometimes continued throughout the day. They were, however, becoming less severe. When free of the headache he feels quite fit. He has also been nervous since the accident and very irritable. There was no question of compensation.

T. K., a male aged 25, was involved in a collision while riding his motor bicycle. Extensive fractures of both frontal bones occurred and he was unconscious for four days. He lay in bed for five weeks and began work two months later. He was examined eight and a half months after the injury and was then still suffering from pains in the head. These were especially noticeable when the weather changed. The pain was throbbing or bursting in character. It was worse on waking in the morning and was aggravated by stooping. It was also aggravated by excitement and was almost unbearable when he attended a football match. Otherwise he felt well and was able to do his work. There was no possibility of any compensation being obtained.

O. T., a male, aged 33, was thrown from his motor bicycle while attempting to avoid a dog. A large fissure-fracture of the left temporal region was apparent on X-ray examination and the patient did not recover consciousness for thirteen days. He lay in bed for three weeks and returned to work four weeks later. When examined six months after his accident he complained of inability to remember about people he knew quite well, and of some difficulty in concentrating. He was not nervous and had been told that he drove his motor bicycle more recklessly than before his accident. He had had practically no headache, whereas before his accident he had suffered from typical migrainous headaches since 1921. These headaches used to be preceded by a visual aura and occurred at least once a week. On the day before examination he had one of these headaches, the first since his accident six months before.

F. B., a male, aged 63, was thrown to the ground by a struggling horse and struck his head on the pavement. He was unconscious for one or two hours. There was bruising over the left parietal and occipital region, but no fracture was apparent on X-ray examination. When examined seven months after his injury he was suffering from a marked degree of loss of memory. He also complained of headaches of great severity which showed no sign of improving. If he stooped to the ground the pain became so bad that he often just lay down on the floor. A spasm of pain occurred during the examination. While it

lasted he remained motionless looking vacantly ahead for a few seconds, and then, when it passed off, had lost the thread of what he was saying. There was no question of compensation.

Three of the above patients had headache of no little severity and many examples in which the headache was of the same type, but of less severity, could be cited. It is noteworthy that no fewer than fifteen of the patients in Group C, although showing certain other symptoms referable to their head injury, had remained quite free of headache since discharge. Some of these were cases of severe injury with extensive fractures of the skull.

Dizziness.—Dizziness is often a prominent complaint after head injury, but its features require careful analysis. The following case records illustrate the types of disturbance included under this term.

J. A., a male, aged 38, fell downstairs and struck his head on the ground. He did not lose consciousness but developed severe headaches which continued until admission to hospital a week later. Lumbar puncture relieved his headache immediately and he insisted on leaving the ward thereafter. X-ray examination demonstrated a fracture in the left parietal region. When examined six and a half months later, there was some loss of memory and the patient had had a few fits. There had been no headache since the lumbar puncture, but the patient complained that if he suddenly rose to his feet or if he looked upwards "his head began to swim."

O. T., a male, aged 38. He was unconscious for thirteen days after his injury. Six months later he noticed slight loss of memory and occasional dizziness. If, while lying on his back, he turned his head to the left or to the right, he complained of his head swimming. The sensation only lasted for a moment and then passed off.

In neither of these cases was there any question of compensation outstanding.

This dizziness was usually a sensation as though the head were "swimming." The patient rarely fell to the ground, but felt that he must steady himself or sit down until it passed off. True vertigo was not present in any of the cases examined. Changes in posture, or movements of the head and eyes were common causes of an attack. The common association of suddenly standing up with the onset of an attack suggests that cerebral anæmia may be a causative factor in some cases, while connection between movements of the head and eyes and the dizziness is suggestive of some disturbance of the labyrinthine mechanism. One patient, for example, who worked in a library, was unable to look up at the upper shelves of books, as this movement of the eyes would cause her to feel so giddy that she felt she might fall. That labyrinthine

damage is a not uncommon result of head injury has been shown recently by Linthicum and Rand [19]. They conclude that there are often disturbances both centrally and in the labyrinthine end-organs.

In the present series, dizziness was noticed in thirty-one cases, as is shown in Table XVIII. The age-incidence is shown in Table XIX.

TABLE XVIII.

Dizziness	Group			Totals
	A	B	C	
Present ..	11	10	10	31
Absent ..	9	17	15	41
Totals ..	20	27	25	72

TABLE XIX.—AGE-PERIODS.

Dizziness	0 to 10	10 to 20	20 to 30	30 to 40	40 to 50	50 to 60	60 to 70	Over 70
Present	0	6	10	4	4	3	2	2
Absent	9	8	15	5	2	0	2	0

These figures include only cases in which post-concussional symptoms were present, but in which no question of compensation was outstanding. They show that there is no great difference in the incidence of this symptom in the different groups. In contrast, however, to headache, the increasing incidence as age advances is a striking feature. The dizziness, though of common occurrence, was usually only slight, and rarely caused by itself any serious incapacity.

Loss of memory and mental ability.—Disturbances of memory and mental ability were often found. With a few exceptions these were slight in degree and caused the patient little inconvenience. They were, however, none the less real and in a few cases the degree of memory loss was great and very incapacitating. The milder degrees were represented by a difficulty in remembering the names of people or of streets which had been formerly well known to the patient. This condition simulates closely the deterioration of memory so often found in old age. In the more severe degrees the changes are more serious. A child who was previously good at school becomes backward, and in adults difficulty in remembering names may be associated with difficulty in recalling

words, so that the patient may complain that he is no longer able to tell a story, or that he makes foolish mistakes in writing a letter. Loss of mental ability to a slight degree was well shown in the case of a shop-assistant who found after his accident that he had difficulty in handling a troublesome customer.

The more severe degrees of loss of memory may even amount to a mild aphasia. This is not surprising when it is remembered that the functions of memory, thought and speech are so intimately dependent on each other that no one of them can be seriously injured without the other two being affected. The loss of memory and mental ability was in some instances so great as to amount to dementia.

O. T. recovered to a remarkable degree from a very severe injury. When examined, however, six months after the accident, he said that he could not concentrate as well as previously and that he had difficulty in "placing" people he knew. He could not remember whether he knew them or not, but if he succeeded in "placing" them in his own mind he remembered their names and all about them.

C. R., a male aged 32, had a collision while riding his motor bicycle and was unconscious for seven days. There was a fracture of the skull in the right parieto-occipital region. When examined four and a half months later the patient was experiencing great difficulty in supervising the fish restaurant which he and his wife managed.

He was unable to recognize people whom he knew well. He would ask his wife the same question repeatedly, having forgotten that she had already answered. His wife was obliged to handle all the money as he could not remember who had paid. He would frequently repeat himself.

He had to avoid stooping as this made his head "swim," and if he looked up or down things seemed to "swim away." He was still suffering from severe headaches. He had completely lost his sense of smell, which was formerly very acute, and he was slightly deaf in the right ear. The patient was taking his case to court, but only to attempt to prove who was responsible for the accident. As, therefore, the degree of incapacity was not the point at issue, there was no reason to suppose that the impending suit had any influence on his health.

The main injury to the brain in this case was probably *contre-coup*, involving the left frontal region in particular.

The frequency of loss of memory and mental ability in the present series of seventy-two cases is shown in Table XX.

In these cases loss of memory must be due to damage to the nervous tissues, and it is therefore not surprising that in Group C this defect is proportionally much higher than in Groups A and B.

TABLE XX.

Memory loss	Group			Totals
	A	B	C	
Severe ..	0	0	4	4
Slight ..	8	4	10	22
None ..	12	23	11	46
Totals ..	20	27	25	72

The influence of age on the incidence of loss of memory is shown in Table XXI.

TABLE XXI.—AGE-PERIODS.

Memory loss	0 to 10	10 to 20	20 to 30	30 to 40	40 to 50	50 to 60	60 to 70	Over 70
Present	2	6	7	3	2	2	3	1
Absent	7	8	18	6	4	1	1	1

This table shows that, as in the case of dizziness, the incidence of loss of memory is higher in the later age-periods, for over 50 per cent. of the cases above 40 years of age had some loss of memory, while in the cases below this age the percentage is 32. This difference is more evident if the cases in Group C (most of which had loss of memory) are omitted, for in Groups A and B taken together, 50 per cent. of the cases above 40 years of age had some memory loss, while in the cases below this age the percentage is 17.

Nervousness.—Nervousness is not uncommonly present after a head injury. It was recorded as a sequel of the injury in 25 cases of the group of 72 in which there was no question of compensation outstanding. The following tables show the incidence of nervousness in the different groups and at the different age-periods.

TABLE XXII.

Nervousness	Group			Totals
	A	B	C	
Present ..	7	7	11	25
Absent ..	13	20	14	47
Totals ..	20	27	25	72

TABLE XXIII.—AGE-PERIODS.

Nervousness			0 to 10	10 to 20	20 to 30	30 to 40	40 to 50	50 to 60	60 to 70	Over 70
Present	..	..	7	8	8	9	1	1	1	1
Absent	..	..	2	9	18	7	5	2	8	1

It is obvious that an increasing incidence of this symptom in the later age-periods, which was such a striking feature of dizziness and loss of memory, is here not evident, in fact the incidence of nervousness is greater in the earlier age-periods. It is a very common sequel in young children. It was present in 35 per cent. of the cases below 40 years of age, while in those above 40 the percentage was only 26.

It is apparent that it cannot be due to recollection of the accident or to any feeling of fear before the accident occurred; indeed the incidents immediately preceding the injury are often not remembered. Abnormal nervousness usually has a purely psychological cause, and there is no doubt that thinking over a severe accident, especially if foolish relatives enlarge on it, is probably sufficient to account for the mental state which is so often found. But as the psychological mechanisms which control behaviour are dependent for their smooth working on the intactness of cerebral connections of great complexity, and as these highest association mechanisms are certainly the most vulnerable, it is difficult to exclude the possibility that the symptom has an organic basis.

It is interesting that in young children a complete change of character is not uncommon after an injury. This may be compared to the disturbances of behaviour which sometimes develop in children after an attack of epidemic encephalitis. It is difficult to prove that these minor disturbances have an organic basis, but it is unjustifiable to assume that their cause is wholly functional.

The following cases illustrate this type of disturbance:—

C. J., a female, aged 7, tripped and fell forward on to her head. She was unconscious for about an hour and there was an extensive fracture of the skull. When examined two months after discharge, her mother said "She doesn't seem to be the same child to me. She's full of mischief. She seems to have the devil in her" (patient smiles). Before her injury she was very quiet and good, now she is disobedient, defiant and daring. She gets very excited and treats younger children badly. She plays all day, but stops to sit down sometimes because of headache. She has become much more nervous, being afraid especially of falling and of the dark.

M. M., a female, aged 9, fell down stairs, but was only stunned for a few seconds. When examined six and a half months later, her mother said she was quite changed. She used to be very good at school, but is now backward and has no interest in it. She is very absent-minded and often forgets what to buy when she is sent a message. She gets so excited sometimes that she "foams at the mouth" while trying to say something, and bursts into tears if she doesn't get what she wants.

Disturbances of sleep.—Difficulty in falling asleep may be a troublesome symptom of the acute stage, and continues in some cases for a long period. This symptom was recorded in nine cases but in most of these it lasted for a few weeks only after the injury.

Epileptic fits.—Epilepsy may develop months or even years after a head injury, and for this reason the present investigation is of little value as far as the frequency of the complication is concerned.

As already mentioned, a convulsion may occur in the early hours after the injury, or several days later. The first convulsion, however, often occurs at an interval of weeks or months after the injury.

These fits may be major or minor in type, and in the latter case it is often difficult to distinguish them from dizzy attacks which are presumably not epileptic manifestations. A point which is of value for their differentiation is that in the case of a dizzy turn the patient himself is conscious of the unpleasant feeling of insecurity it gives, while in the case of a *petit mal* attack, the patient is less disturbed by it, and indeed is often unaware that anything untoward has occurred.

Fits were recorded as having occurred in eight cases, one of which was in Group A, four in Group B and three in Group C.

Physical examination.—Physical examination usually elicited no abnormal signs. Anosmia and deafness were occasionally present, as were slight motor disturbances such as tremor or unsteadiness of movement. In one case progressive deafness and unsteadiness had developed, due presumably to labyrinthine disturbances.

One patient complained that she could no longer take wine as it "went to her head" at once. Another noticed that since the injury his hands perspired excessively, while a third had developed diabetes insipidus, which was due presumably to a lesion of the hypothalamus.

SUMMARY OF LATER SYMPTOMS.

As was shown in Table XV, 86 patients—that is 61 per cent. of the 141 cases which were examined at an average interval of six months after discharge from hospital—complained of symptoms which were

referable to the injury they had received. As in 14 of the 86 cases the question of compensation was outstanding, these were excluded from the analysis of symptoms. There remained, therefore, 72 cases in which post-concussional symptoms were present and could be analysed. The relative frequency of the more common symptoms is shown in Table XXIV.

TABLE XXIV.

Symptoms	Number of cases in which symptoms were noted	Percentage of the total of 72 cases
Headache	41	57
Dizziness	31	43
Loss of memory ..	26	36
Nervousness	25	34
Sleeplessness .. .	9	13

Fifty-seven of the 72 cases were below the age of 40, and 15 were above this age. Headache and nervousness were more often noted in the younger age-periods, while dizziness and memory-loss were more often present in cases above the age of 40 years.

DISCUSSION OF POST-TRAUMATIC DISTURBANCES.

The principal symptoms which may be present after head injury are headache, giddiness, loss of mental ability, disturbance of sleep, and epilepsy. All degrees of disturbance are met with, and the duration of the symptoms may be a few days only, or may cause incapacity for months or years. Whether the disturbances are slight or severe, the individual symptoms are remarkably similar in each case.

The loss of memory must have an organic basis, and the same may be said of post-traumatic epilepsy. All the nervous elements within the brain may be damaged in severe head injuries, and where loss of memory is present it may be assumed that a number of the nerve-cells or their processes have been so severely injured that their recovery is impossible. Multiple capillary hæmorrhages may contribute to the damage of nervous tissue, but it is unjustifiable to assume, even when no hæmorrhage or contusion is apparent, that the nerve-fibres have escaped. That the degree of damage may be extensive is apparent from encephalographic studies, such as those of Foerster and Bielschowsky [11], [4].

Recent investigations on the pathology of concussion indicate that the degree of injury to the brain has in the past been under-estimated.

Meyer, in 1904 [22], demonstrated multiple areas of softening in cases of traumatic insanity, and other workers have shown pathological changes in comparatively mild degrees of concussion. Thus, Cassasa [6] described multiple hæmorrhages scattered throughout the brain, and Trotter [34] has shown that areas of "unresolved contusion" may be present. Minkowski [23] has studied the finer pathological changes, especially the damage to small blood-vessels. Martland and Beling [21] have shown that multiple hæmorrhages are only present in a small proportion, 2.9 per cent., of fatal cases, and that the commonest gross lesion is a *contre-coup* laceration which was present in 57 per cent. of their series of 309 autopsies. Martland [20] has drawn attention to the condition which he calls "punch drunk," in which professional boxers develop symptoms which indicate degenerative changes in the brain. These include slowness of movement, hesitancy of speech, tremors of the hands, dragging of one or both legs, staggering, Parkinsonism, vertigo and deafness. Many cases ultimately develop marked mental deterioration, and end their days in mental hospitals. Martland suggests that the changes are due to multiple capillary hæmorrhages, such as have been shown by Cassasa [6] to occur in comparatively mild injuries.

Rosenhagen in 1930 [28] drew attention to fine cellular changes in cases of concussion. A question which arises in connection with this work is whether these changes have not been due to some complicating factor, such as hyperthermia before death. In one of Rosenhagen's cases, however, death occurred suddenly eight weeks after the injury, and in the interval the patient, though suffering from headache, had been able to return to work. Then he suddenly developed hemiplegia and died in eight hours from the effects of cerebral hæmorrhage. Rosenhagen found extensive degenerative changes of a fatty nature in both the ganglion and neuroglial cells, which he concluded were due to the previous head injury. Symonds [33] has also emphasized the importance of considering the direct injury which is caused to the neural tissue at the time of the accident.

Penfield [26] has laid stress on the formation of scar-tissue as a cause of traumatic epilepsy, and has followed the stages of astrocytic scar formation in experimental work. Linell [18] has confirmed his observations.

It is surprising that, in spite of Penfield's important work, the investigation of the glial reaction has been largely neglected in human pathological material. It is recognized that extensive gliosis must

occur in areas in which the brain tissue is totally or partially destroyed, and the failure of other workers to demonstrate these changes in fatal cases must be due to the unsuitability of their material for study. Penfield [26] and Linell [18] have shown that the glial activity begins three days after the injury, and reaches its maximum in three weeks; thereafter, the fibres having been formed, the cells retrogress, so that at an interval of six weeks after the injury there are few cell bodies to be seen. Death must therefore occur several days after the accident for these changes to be demonstrable in the human brain, and it is uncommon at this stage except in the case of meningitis supervening.

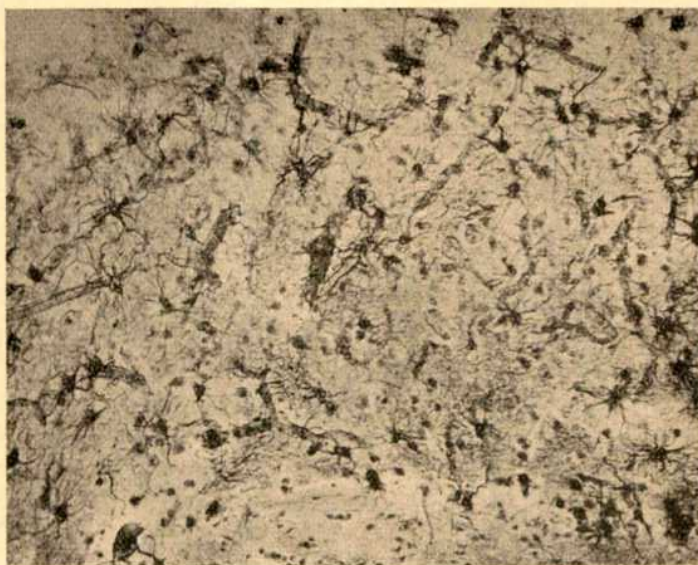


FIG. 8.—Shows reaction around a small hæmorrhage in the sub-cortical white matter due to injury, three weeks before death. Numerous new capillaries are present and the astrocytes are large and numerous. The latter are of the "fibrous" type and are in an active stage of reproduction. (The blood clot was situated at the upper left corner of the field shown.) Frozen section impregnated by Cajal's gold chloride sublimate method $\times 120$.

I have had the good fortune to obtain the brains of three cases which have died at an interval of two to three weeks after injury. In two of these death was associated with meningitis, but in the third there was no meningeal infection. In all three the astrocytic reaction was very striking. The fibrous and protoplasmic astrocytes were equally affected, and their activity was apparent far beyond the area of gross cerebral contusion. As is shown in fig. 8, the reaction was pronounced around a small intracerebral hæmorrhage, but it extended

far beyond it. As Penfield has shown, the presence of necrotic brain tissue is a stimulus to the proliferation of the glia, and the widespread astrocytic reaction in this case provides evidence that the destruction of nervous tissue may be more extensive than is apparent at first sight, and that nervous tissue may be damaged in regions where the brain on ordinary microscopical examination appears to be normal.

In attempting to provide a pathological explanation of such symptoms as headache and dizziness it is important to realize that within the skull there are two circulatory systems, that of the blood and that of the cerebrospinal fluid. These two circulations are dependent to a great extent on each other, and whatever the exact mechanism of their control, it is a mechanism of great delicacy. There is evidence that these circulations are both disturbed in some of the states which follow head injury. Bielschowsky [4] has shown that in post-concussional disturbances the pressure of the cerebrospinal fluid may be abnormally high, or abnormally low, and that the rate of absorption of the fluid is often reduced, as is evidenced by the slow rate at which sodium iodide is removed after injection into the subarachnoid space. Bielschowsky concludes his paper with the following sentence:—

“Bei 106 Fällen von Kopftraumen verschiedenster Art und Schwere mit und ohne cerebrale Hirnerscheinungen finden sich in der überwiegenden Mehrzahl der Fälle mehr oder weniger ausgeprägte Störungen des Liquorsystems.”

Muck [24, 25] has made the interesting observation that the blood-vessels of the nasal mucosa in cases showing post-concussional symptoms are often abnormally irritable, and as both they and the pial vessels have a common nerve supply, he concludes that the pial vessels are also in an abnormal state.

Certain features of the headache and dizziness also suggest circulatory disturbances. Its aggravation by conditions which physiologically raise the intracranial pressure, as stooping, exertion and sleep, is a definite feature of the headache, while dizziness is sometimes produced by conditions which lower the intracranial blood-pressure, such as the sudden assumption of the erect posture. There are, however, other causes of dizziness; some are probably associated with labyrinthine disturbances, and indeed Linthicum and Rand [19] have recently shown that abnormalities of the vestibular reactions are not uncommon in patients suffering from post-concussional disturbances of this type.

It seems therefore probable that symptoms such as headache,

dizziness and sleeplessness, depend in many instances on disturbances of the intracranial circulations. The slow disappearance of such symptoms probably indicates that the delicate adjustments of intracranial circulation are slow to recover. Further, the not uncommon observation that after apparent recovery excitement or effort may cause a return of headache, indicates that recovery may be more apparent than real.

DIAGNOSIS, PROGNOSIS AND TREATMENT.

It seems desirable, finally, to consider in what way the above conclusions can be applied to the practical aspects of the subject.

Diagnosis.—In the discussion of post-concussional disturbances, reasons have been given for concluding that the symptoms must have an organic origin and cannot be dependent on any functional disturbance. It is therefore important to note the exact features of these symptoms in order that they may be distinguished from psychogenic disorders.

The occurrence of epileptic attacks provides definite evidence of considerable damage, as also does the demonstration of loss of memory.

The careful analysis of headache and dizziness provides the best guide to their nature. Their association with changes in posture and conditions which physiologically alter the intracranial pressure are points of diagnostic value. Physical examination alone seldom provides evidence of cerebral injury even when its extent is considerable, and the diagnosis of organic injury to the brain must be therefore arrived at mainly by questioning the patient with a view to eliciting the exact nature of his complaints. It is only by so doing that an approximately correct idea can be obtained with regard to the relative degree of organic and functional disturbance.

Prognosis.—The factors influencing prognosis in the acute stage have already been considered

One of the objects of this investigation was to investigate the possibility of recognizing in the acute stage cases in which late disturbances would develop. It must be admitted that in this respect the results have been disappointing; no means have been found by which an accurate prognosis with regard to the possibility of the development of post-concussional symptoms can be formed.

There are, however, one or two factors which do undoubtedly influence the ultimate outlook. The first of these is the age of the patient; patients above the age of 40 or 50 are much less likely to

recover fully than are those below this age. Secondly, the degree of injury as estimated by the duration of unconsciousness is an indication of some, though of surprisingly little, value. For example, gross degrees of mental defect were found only in young people whose cases fell into Group C.

Treatment.—The modern treatment of cases of head injury has been directed largely towards reducing intracranial pressure. As soon as the initial stage of shock has passed off, the patient is propped up in the Fowler position and given a dose of calomel. The intake of fluid is restricted, intravenous injections of hypertonic solutions are given and lumbar puncture is carried out repeatedly.

This line of treatment is based on the assumption that cerebral oedema is a dangerous complication in that it may lead directly to death through raising the intracranial pressure, and that it is the cause of prolonged unconsciousness. Cerebral oedema is a constant development in cerebral contusion, but is it often a dangerous complication?

A rise of intracranial pressure may certainly be caused by oedema of the brain, but in the present series the pressure was seldom above 300 mm. of water, and was therefore quite low when compared to the pressure readings which are commonly found in diseases such as meningitis and cerebral tumour. There was no evidence that in any of the fatal cases death was due to increased intracranial pressure.

It is probable that cerebral oedema can prolong the duration of loss of consciousness. The evidence in favour of this is that dehydrating measures may hasten the return of consciousness. It is, however, at least questionable whether an early return of consciousness is desirable in severe injuries, and if the cerebral tissues are really damaged by being oedematous.

It is important to bear in mind that a degree of increase of intracranial pressure provides a powerful means of controlling hæmorrhage from torn cerebral capillaries and veins. In this way, cerebral oedema may prevent hæmorrhage, and correspondingly the artificial reduction of intracranial pressure may aggravate it.

For these reasons it seems that treatment by reduction of intracranial pressure should be reserved for cases which provide a definite indication for it, and that its indiscriminate use is not only undesirable, but dangerous.

Details of treatment.—In the early stages of severe injuries, treatment is mainly directed towards combating shock. When unconsciousness is profound, there is a real danger, if the swallowing reflex

has not recovered, that blood and nasal secretions may be inhaled into the lungs. This can be avoided by turning the patient half over on his face. As soon as the stage of shock has passed, there seems no reason why the patient should not be allowed a pillow: patients often complain bitterly of the discomfort caused by lying on a hard mattress and this undoubtedly contributes to restlessness in some cases. Retention of urine is also a common cause of restlessness.

For the reasons stated in the last section, it is usually undesirable to attempt to reduce cerebral œdema during the first day or two days. In my opinion, it is more important that some means should be found of preventing violent restlessness, as this is liable, by raising the blood-pressure, to encourage hæmorrhage from torn cerebral capillaries and veins. Morphia is useful for this purpose and can apparently be given without danger, provided the patient is allowed to recover from the influence of the drug between each dose, so that any change in his degree of consciousness is not obscured.

Whether in severe cases some cerebrospinal fluid should be withdrawn is a difficult question to decide. In the first place, it is no easy matter to perform a lumbar puncture on a violently resistive person, and the presence of blood in the cerebrospinal fluid makes the back rigid and sensitive, as in cases of meningitis. A struggle is inevitable in many cases, and this may do more harm than the lumbar puncture would do good. This difficulty may, however, to a great extent be avoided by carrying out the procedure after the administration of morphine. In favour of lumbar puncture is the fact that removal of a small amount of cerebrospinal fluid not infrequently gives relief to headache, and seems in some patients to hasten mental recovery. In only five cases in a series of twenty-five was the clinical condition on the day following lumbar puncture not definitely improved, and in a few relief from severe headache was quite dramatic.

It may perhaps be fairly stated that if loss of consciousness is prolonged beyond two days, if headache is severe, or if the condition is getting worse, withdrawal of some cerebrospinal fluid is of value both for diagnostic and for therapeutic purposes. It is better to relieve cerebral œdema by lumbar puncture than by the use of hypertonic solutions, because with lumbar puncture the pressure of the fluid can be estimated and care can be taken to avoid reducing the pressure below normal. It therefore forms a more precise and a safer method of treatment.

Lumbar puncture is not only of value as a method of treatment, but

it can provide an accurate indication of the intracranial pressure and of the degree of any subarachnoid hæmorrhage. It also gives the first evidence available of the onset of meningitis. Further, the irritating effect of blood in the subarachnoid space, which in some cases is great, may be reduced by the withdrawal of some of the blood-stained fluid.

Where the pressure is high, the effect of withdrawing a little cerebrospinal fluid may be supplemented by administering a purge or by raising the patient into the Fowler position.

In the absence of a depressed fracture, there are few indications for operation on the skull. Compression of the brain by hæmorrhage from the middle meningeal artery is a rare complication and is not usually difficult to diagnose. The gradual accumulation of blood in the subdural space may require surgical relief weeks or months after the accident, but rarely in the acute stage.

A very gradual return to normal activity is perhaps the most important point in the treatment of the convalescent stage. A recurrence of symptoms often indicates that work has been resumed too soon. No two cases are alike, and each patient must find out for himself how quickly he can with impunity return to full work.

An important part of the treatment is to endeavour to adjust the patient's mental attitude to his injury. He frequently leaves hospital after a week or ten days, may or may not rest for a time at home, and then is distressed to find that when he begins to work he develops headache and giddiness. He then fears that there has been some damage to his brain and is afraid to "sign off" his compensation claim. These worries, combined with the demoralizing effect of severe headache, provide the basis necessary for the development of a condition of traumatic neurasthenia. Further, if the skull has been fractured, the patient has a dread lest another slight injury to his head may have serious consequences, and therefore, if his occupation is a dangerous one, such as mining, he is afraid to resume it again. It is especially in the case of industrial accidents that great care should be taken to adjust the patient's attitude to his injury. It is inadvisable to minimize the accident unduly; it seems wiser in the first place to tell the patient that complete recovery will occur, but that he must make up his mind to be off work for several weeks or months, that recovery is always gradual, and that he must return to his full activity slowly. If he develops a headache or feels giddy, that must be looked on as an indication that he has done more than he is yet fit for.

If this attitude is adopted by the surgeon, an intelligent patient will realize the position and will not be frightened by the occurrence of an occasional attack of headache. Traumatic neurasthenia in a patient is largely caused by fear—fear that he is not getting better, fear that he will never be fit for work, fear that his brain is damaged, fear that another head injury would be fatal, and so on. For these reasons, simple explanations directed towards adjusting the patient's attitude to his condition form a most important factor in the treatment of industrial accidents, not only those which involve the skull, but also those involving all parts of the body.

If the patient returns at an interval after the injury complaining of severe post-concussional symptoms, the treatment advised by Trotter is of great value and often leads to a complete cure. Rest in the Fowler position both day and night, combined with the use of dehydrating measures such as the regular administration of strong solution of magnesium sulphate, either orally or by the rectum, is the basis of this treatment. Its success in many cases suggests that circulatory disturbances, such as Trotter describes, are an important factor in causing the persistence of symptoms.

Examination of the patient in the acute stage.—Cases of head injury when first seen by the surgeon are often in a state of severe shock, and in such circumstances it is desirable that physical examination should be no more than is absolutely necessary. This preliminary examination should be directed in the first place towards estimating the degree of injury and the immediate prognosis, but should also be carried out in sufficient detail to enable the subsequent development of complications to be recognized.

Death occurring during the first forty-eight hours is usually associated with a failure to react from the initial shock. As this is indicated by a progressive increase in the rate of the pulse and respirations, the importance of recording the pulse, respiration and temperature at short intervals is evident.

Careful examination for hæmorrhage from the ears, nose and throat is important because of the frequency with which infection may reach the brain through these avenues in the case of fracture of the base of the skull.

Wounds of the scalp should be treated with scrupulous care, however small they may be; the danger of infection is shown by one case in which a wound of the forehead less than an inch in length resulted in a fatal osteo-myelitis of the underlying skull.

The importance of recognizing hæmorrhage from the nose in the case of comatose patients, because of the danger of aspiration of blood and secretions into the lungs, has already been stressed.

From the practical standpoint, it is desirable to examine the nervous system of the patient as soon as possible after admission, in order that changes which may indicate the onset of serious complications may be recognized at a subsequent examination. It is therefore necessary to bear in mind the chief complications which may contribute to or cause death:—

- (1) Aspiration of blood and nasal secretions into the lungs,
- (2) Infection spreading to the meninges and brain.
- (3) Cerebral œdema.
- (4) Intracranial hæmorrhage: epidural, subdural, subarachnoid, intracerebral.

The onset of intracranial complications other than those due to infection manifests itself principally by a deepening of the degree of unconsciousness, and by the onset of evidence of local damage to the brain, the most important of which is the development of weakness of one side of the body.

The stages by which consciousness returns have already been described, and their importance lies in the necessity for recognizing the changes that indicate respectively either that consciousness is returning or that the patient is becoming more unconscious.

SUMMARY.

It is difficult to summarize the points which have been discussed in this paper. The study of the two hundred cases dealt with has provided material for investigation, of which only certain aspects have been analysed.

The frequency with which the common symptoms and signs of concussion occur has been analysed, and their significance discussed. Changes in the pressure, cytology and chemistry of the cerebrospinal fluid have been investigated in a series of severe cases, and have thrown light on the significance of certain symptoms and signs of the acute stage.

The mechanism by which the brain is damaged in injuries of the head has been discussed, and conclusions have been arrived at with regard to the mechanism of loss of consciousness and *contre-coup* injury. The pathology of the condition called "cerebral irritation" has also been considered. The conclusions arrived at in this section are contrary

to most current teaching. The cases in Group C provide material for study of the stages by which consciousness returns.

Most of the cases seen in the acute stage have been re-examined later. The fact that in the series compensation cases are few in number has greatly added to the value of this part of the work. The frequency with which post-concussional disturbances occur has been investigated. Physical examination alone is of little value in the attempt to estimate the degree of cerebral damage, and hence the detailed analysis of the subjective features of genuine post-concussional disturbances is important.

The investigation of post-mortem material forms a small section of this work; marked changes in the neuroglia have been demonstrated in the brains of cases dying at an interval after the injury.

Finally, the practical application of certain aspects of this work has been discussed in relation to diagnosis, prognosis and treatment.

The subject of this paper suggests many lines of investigation, and the work which is here recorded must be regarded merely as a preliminary report based on the first two hundred cases seen.

In conclusion, I wish to express my gratitude to the Surgical Staff of the Royal Infirmary for allowing me to study the cases under their charge, and to the Residents and Nursing Staff who have been invariably helpful. I have also to thank the Medical Research Council for a grant for the purpose of this investigation.

REFERENCES.

- [1] BAGLEY, C. *Arch. of Surg.*, 1929, **18**, 1078.
- [2] *Idem.* "The Intracranial Pressure in Health and Disease." Association for Research in Nervous and Mental Diseases. Baltimore, 1929, p. 217.
- [3] BERNER, O. *Virchow's Archiv*, 1930, **277**, 386.
- [4] BIELSCHOWSKY, P. *Zeitschr. Neurol. u. Psychiatr.*, 1928, **117**, 55.
- [5] BOLLINGER, O. *Internat. Beitrage zum Wissenschaft Med.*, 1891, **2**, 57.
- [6] CASASAS, C. B. *Proc. Path. Soc.*, N.S., 1924, **24**, 101.
- [7] CUSHING, H. *Amer. Journ. Med. Sci.*, 1902, **124**, 875.
- [8] *Idem.* "Studies in Intracranial Physiology and Surgery." London, 1926.
- [9] DANDY, W. E. *Ann. Surg.*, 1918, **68**, 569.
- [10] *Idem.* *Ibid.*, 1920, **70**, 129.
- [11] FOEBSTER, O. *Zeitschr. Neurol. u. Psychiatr.*, 1924, **94**, 512.
- [12] FOEBSTER, O., and PENFIELD, W. *Brain*, 1930, **53**, 99.
- [13] GREENFIELD, J. G., and CARMICHAEL, E. A. "The Cerebrospinal Fluid in Clinical Diagnosis." London, 1925, 49.
- [14] HURST, E. WESTON. *Journ. Path. and Bact.*, 1932, **35**, 41.
- [15] JACKSON, H. *Surg. Gynecol. and Obstet.*, 1922, **34**, 494.
- [16] JEFFERSON, G. Communication to the Royal Society of Medicine, December 4, 1931.
- [17] KUBIE, L. S. *Arch. Neurol. and Psychiatr.*, 1926, **16**, 319.
- [18] LINELL, E. A. *Ibid.*, 1929, **22**, 326.
- [19] LINTHICUM, F. H., and RAND, O. W. *Arch. Otolaryngol.*, 1931, **13**, 785.

- [20] MARTLAND, H. S. *Journ. Amer. Med. Assoc.*, 1928, **91**, 1108.
 - [21] MARTLAND, H. S., and BELING, C. O. *Arch. Neurol. and Psychiatr.*, 1929, **22**, 1001.
 - [22] MEYER, A. *Amer. Journ. Insan.*, 1904, **60**, 874, 877, 882 and 888.
 - [23] MINKOWSKI, M. *Schweis. Med. Wochenschr.*, 1930, **11**, 701.
 - [24] MUCK, O. *Zeitschr. Neurol. u. Psychiatr.*, 1926, **106**, 351.
 - [25] *Idem. Ibid.*, 1928, **115**, 581.
 - [26] PENFIELD, W. *Brain*, 1927, **50**, 499.
 - [27] RAND, O. W. *Amer. Journ. Surg.*, 1930, **8**, 772.
 - [28] ROSENHAGEN, H. *Deutsch. Zeitschr. f. Nervenheilk.*, 1930, **114**, 29.
 - [29] *Idem. Klin. Wochenschr.*, 1930, No. 13, p. 55.
 - [30] ROUGHHEAD, W. "The Trial of John Donald Merritt." Edinburgh, 1929.
 - [31] SOMERVILLE, O. W. *Trans. Med. Chir. Soc. Edin., Edin. Med. Journ.*, 1931, **38**, No. 8.
 - [32] SYMONDS, O. P. *Brit. Med. Journ.*, 1928, **11**, 829.
 - [33] *Idem. Lancet*, 1932, **1**, 820.
 - [34] TROTTER, W. *Brain*, 1919, **42**, 353, p. 2.
 - [35] *Idem Lancet*, 1924, **1**, 985, p. 53.
 - [36] *Idem. Ibid.*, 1925, **11**, 953, p. 2.
 - [37] WEED, L. H. *Physiol. Review*, 1922, **2**, 171.
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NOTICES OF RECENT PUBLICATIONS.

Poliomyelitis. A Summary by the International Committee for the Study of Infantile Paralysis. Pp. 562. Baltimore: Williams and Wilkins. 1932. Price \$6.

In 1928 an International Committee was appointed in America with adequate financial support to study poliomyelitis. A number of contributions by individual members of the Committee have already appeared in the medical press, but this large volume represents the chief results of its work during the past four years. It is properly described as a survey, for it contains little that is not already familiar to students of the subject, but on the other hand it reviews very fully the literature on all aspects of the disease, and will therefore prove useful to anyone interested in poliomyelitis who has not time to consult original sources, or the training necessary to evaluate critically the numerous contributions to its ætiology and epidemiology particularly.

At present when epidemics are occurring in various parts of the world the main points of interest are its epidemicity, and the most promising treatment of the disease in its early stages. On the former question no new conclusions are drawn, but a very complete survey of the experimental work of the last twenty years is given. The most important statement in the chapter on treatment is that there is nothing to indicate a therapeutic value in the serum of convalescents, either in reducing fatality or in preventing the development of paralysis; this conclusion is drawn from the study of more than 1,000 cases diagnosed in the preparalytic stage, half of which were treated by serum, the other half being controls. Applications of X-rays to the spine, a method of treatment that had promised to become popular, may be, if observations on experimental animals are relevant, actually harmful.

This volume is a valuable contribution to the literature of the disease, but would have been more useful if a critical summary of each section or chapter had been provided.

Acromegaly. By F. R. B. ATKINSON. Pp. 260. London: Bale, Sons and Danielsson. 1932. Price 21s.

For many years the author has been collecting the records of all cases of acromegaly published in medical literature, and this monograph details the symptoms and the associated anatomical changes from records of 1,319 clinical descriptions and 265 post-mortem examinations. His method has been to accept and enumerate without any attempt at critical analysis the changes in structure and function mentioned by the authors and in this way to present all the symptoms which may occur in the course of the disease. This method deprives part of his work, and particularly that devoted to the pathology of acromegaly, of the value it might otherwise have, for obviously the structural changes described by earlier authors are of little value as compared with results

of examination by modern methods; but on the other hand his unbiased summary of all the main features of the disease will be useful to anyone engaged in research on any aspect of it.' This is facilitated by tables in which the chief features of all the recorded cases are given concisely, and by a very extensive bibliography.

Diagnostik der Hirngeschwülste. von K. GOLDSTEIN und H. COHN.
S. 138. Berlin: Urban und Schwarzenberg. 1932. Price M. 12.

The first half of this volume is devoted to descriptions of the symptomatology and to the various methods of investigation of cerebral tumours. Adequate emphasis is laid on the observation and interpretation of clinical signs, but a large part of this section is reserved for accessory methods of diagnosis, as radiological and ventriculographical examination and brain puncture, a method little used in England, and, according to the authors, rightly so as it may bring about unpleasant or dangerous complications. In the remaining chapters the symptoms of, and the signs produced by, tumours in different regions of the brain are discussed fully. The authors have evidently had considerable personal experience of the subject on which they write, but this monograph is largely based on cases recorded in the literature; there are over 700 references. This is to some extent necessary as few have the individual experience essential for an adequate presentation of such a large and complex subject, but it deprives the book of much of the value it would have if it were written mainly from the observations of too such well known neurologists. The acceptance without due critical evaluation of many references may throw doubt on some of their conclusions, but the book can be recommended as one of the most concise, up-to-date and readable monographs on tumours of the brain.

Ueber die Schädelperkussion. von L. BENEDEK. S. 112. Berlin:
S. Karger. 1932. Price M. 6.

The author starts with the assumption that tumours and other lesions raising intracranial pressure frequently alter the physical properties of the skull, and therefore modify the normal percussion note. In order to obtain uniformity he employs for percussion where possible a complicated apparatus driven by an electric motor and a form of microphone to augment or to record graphically the note produced by percussion. As this depends partly on the thickness of the skull, it is necessary to measure this by another instrument after a trephine opening has been made; charts are printed to show the variations in thickness in different regions, and from these the thickness in any place can be determined approximately if one measurement is available. By changes in the percussion note recorded and measured by these means the author claims that he is able to localize accurately tumours and other intracranial lesions. The introduction of any reliable technique which can aid in diagnosis must be welcome, and, though the claims made for this procedure are not convincing, the book therefore deserves notice.

Les Séquelles de l'Encéphalite épidémique. Par G. GUILLAN et P. MOLLARET. Pp. 103. Paris: G. Doin et Cie. 1932. Price Fr. 28.

In this small volume the sequels of epidemic encephalitis are described purely from the nosological point of view, without, in most instances, any attempt to analyse their nature or to determine the anatomical lesions with which they are associated. The clinical descriptions are adequate and are copiously illustrated by photographs. The short section on treatment presents no new therapeutic measures of promise.

Handbuch der Geisteskrankheiten. Herausgegeben von OSWALD BUMKE. Neunter Band. Spez. Teil 5. Die Schizophrenie. Redigiert von K. Wilmanns. S.783, mit 99 Abbildungen. Berlin: Springer. 1932. Price Rm. 86.00.

This volume completes the thorough and learned exposition of modern psychiatry which has been issued under Professor Bumke's general editorship during the past four years. Actually the present volume is edited by Professor Wilmanns of Heidelberg; all its contributors are or have been his colleagues, and is appropriately dedicated to Jaspers, whose teaching has so greatly influenced this work. The clarity and range of the presentation show the wisdom of entrusting so difficult a subject to a group of workers with a common point of view. They regard schizophrenia as a collection of symptom-complexes which, with our present knowledge, cannot be further differentiated, and the psychological method of research appears to them the most fruitful now at our disposal.

The book commences with an informative historical chapter by Hans Grubbe; he is, however, unfair in his reference to Henry Maudsley, and he says nothing of Adolf Meyer. The ætiology of schizophrenia is considered in a series of papers by Beringer (Heredity and Mental Constitution) and Mayer-Gross (General Factors, such as Race and Sex, and Somatic and Psychic Traumata).

Then comes the general symptomatology: Grubbe deals with psychopathology; a brilliant section on motor manifestations is the work of the late August Homburger; and Steiner and Strauss present such physical findings as have been reported.

The clinical section, which has been written by Mayer-Gross, takes up more than a third of the whole volume. It is an erudite and thorough account, based on a great deal of original observation and giving evidence of that minute psychological study which can best be described as phenomenological. The mode of onset, the typical syndromes, atypical forms and course of the illness are given at length, followed by brief sections on diagnosis and treatment. This last therapeutic section is only ten pages long and bespeaks honest scepticism rather than vague or enthusiastic hope. A curt negative section on morbid anatomy by Steiner, a lengthy and interesting survey of the social

aspects of the disorder by A. Wetzel, and a well-documented examination of the artistic productions of schizophrenics by Burger-Prinz (who is here heavily in the debt of Prinzhorn) are followed by a résumé of the general theory of schizophrenia, with a personal contribution by Gruhle, which concludes the book except for a full bibliography and index. There is no other work on schizophrenia which can compare with this for fullness and accuracy.

The Gestalt Theory and the Problem of Configuration. By BRUNO PETERMANN. Pp. 344. London: Kegan Paul. 1932. Price 15s.

"Gestalt" psychology has assumed so important a place among current schools that this well-informed and critical survey is welcome. It is, therefore, unfortunate that its style should be very difficult, a fault for which neither the subject-matter nor the translator can justly be held to blame. Many will regret that the Wertheimer-Koffka-Köhler theory has been chosen almost exclusively for consideration; a fuller presentation of the work of Krueger's associates would have added greatly to the value of this book. Dr. Petermann finds fault with the concepts of the "Gestalt" theory rather than with its experimental data. He concludes that the vice of the theory must invalidate the attempts at appraising the phenomena. His reasons for this are partly philosophical, partly scientific, in both cases very technical and involved.

Biologische und "reine" Psychologie im Persönlichkeitsaufbau. von G. EWALD. S. 138. Berlin: Karger. 1932. Price Rm. 14.40.

With the increasing emphasis that is being laid on personality, there is need for such thoughtful essays as this of Professor Ewald. He takes trouble to make his meaning clear, he draws a useful distinction between character and temperament and related concepts, and insists, as a psychiatrist should, that the study of personality is not complete when it considers only psychic data. The somatic and genetic factors in personality are not negligible; only a total or biological approach to the problem can do justice to it. Ewald's studies in this field, formerly out of season amid the "dynamic" psychological welter, are now likely to receive temperate consideration such as their sobriety and critical recognition of the modern position deserve.

Psychodiagnostik. von HERMANN ROBSCHACH. Zweite Auflage. Pp. 280 + Tafeln. Bern and Berlin: Hans Huber. 1932. Price Sv. Fr. 18.

The Rorschach method of investigation has been applied widely and not always cautiously to the study of psychopathological problems. The unfortunate death of its brilliant originator left the method incomplete on the interpretative side, but sufficient had been done before his death to establish its main lines, and subsequent work has demonstrated its value within a limited field. The present excellent production is an unaltered reprint of the first

edition, issued in his lifetime, with a supplementary essay which was published after his death. The second volume contains durable reproductions on cardboard of the ink-bLOTS used as perceptual material.

Die vierfache Muskelinnervation, einschliesslich der Pathogenese und Therapie der progressiven Muskeldystrophie. von KEN KURÉ.
S. 320. Berlin: Urban und Schwarzenberg. Price M. 20.

In this book the author elaborates his well-known thesis that voluntary muscle is innervated by nerves related to four different systems, the pyramidal, extra-pyramidal, sympathetic and para-sympathetic, and that muscular tone is of three kinds, cerebrospinal, sympathetic, and para-sympathetic. Of these the first is probably comparable to Sherrington's contractile tonus, and the two last to plastic tonus. The nutrition of voluntary muscle is governed by all these systems to some extent, but especially by the sympathetic and para-sympathetic, and it is to lesions of the latter that muscular dystrophies are due. This thesis is supported by a number of experiments and post-mortem examinations. Cases of muscular dystrophy have also been treated with adrenaline and pilocarpine to replace the lost nervous impulses, and good results are claimed for this treatment.

These views have already been challenged by orthodox physiologists as they have appeared in individual papers during the last ten years, and many points are still in dispute. The present volume is rather a re-statement of the author's position than an attempt to answer the arguments of his critics.

Die Einteilung des Nervensystems nach seinen Leistungen. von L. R. MÜLLER. S. 74. Leipzig: G. Thieme. 1933. Price M. 6.80.

In this popular but interesting presentation of his views on the mode of action of the nervous system the author studies in succession those parts concerned in determining our reactions to our surroundings ("systema pro mundo"); those which maintain muscle tone and the postures of our bodies ("systema myotonicum et myostaticum"), and those belonging to the so-called autonomic systems which regulate visceral, vascular and other primitive activities ("systema vitale"). He discusses in turn the nature and activity of each of these three systems and in doing so brings out many important points. The "vital system," on which he is a recognized authority, is treated in greatest detail and its relations to the rest of the nervous system, as well as its essential differences, are emphasized. In such a study where general statements are unavoidable the reader will necessarily find points on which he cannot agree with the author, and in places may be even unable to accept his premises, but the book is instructive in that in many respects it presents a new point of view.

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EDITOR.